# FORMULATION AND DEVELOPMENT OF OLMESARTAN MEDOXOMIL IMMEDIATE RELEASE TABLETS

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# INDEX

# LIST OF ABBREVIATIONS

| Symbols | | Abbreviations |
|---|---|---|
| BCS | - | Biopharmaceutical Classification System |
| DDS | - | Drug Delivery System |
| RMG | - | Rapid mixer granulator |
| FBP | - | Fluidized Bed Processor |
| FDA | - | Food & Drug Administration |
| GIT | - | Gastro Intestinal Tract |
| HCl | - | Hydrochloric acid |
| HPC | - | Hydroxy Propyl Cellulose |
| HPLC | - | High Performance Liquid Chromatography |
| MCC | - | Microcrystalline cellulose |
| MC | - | Methyl Cellulose |
| NaOH | - | Sodium Hydroxide |
| NCC | - | No Chemical Change |
| NLT | - | Not less than |
| NMT | - | Not more than |
| NSAIDs | - | Non Steroidal Anti Inflammatory Drugs |
| PVP | - | Polyvinyl Pyrrolidone |
| TI | - | Therapeutic Index |
| USP | - | United States Pharmacopoeia |
| ACE | - | Angiotension converting enzyme |
| ARBs | - | Anti receptor blockers |

**Symbols:**

| | | |
|---|---|---|
| # | - | mesh |
| % | - | Percentage |
| Θ | - | Angle of repose |
| w/w | - | weight by weight |
| v/v | - | volume by volume |
| min | - | minute |
| sec | - | second |
| mg | - | milligram |
| gms | - | grams |
| mm | - | millimeter |
| nm | - | nanometer |
| µm | - | micrometer |
| µl | - | microlitre |
| rpm | - | rotations per minute |

# INTRODUCTION

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. The term compressed tablet is believed to have been first used by 'John Wyeth and Philadelphinn'. During the same period molded tablets were introduced to be used as Hypodermic tablets for injections.

Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [eg. simplicity & economy of preparation, stability and convenience in packing, shipping, and dispensing] and the patient [eg. accuracy of dosage, compactness, post ability, blendness of taste and ease of administration].

Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.

**Tabletting formulations:**

In the tablet-pressing process, it is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in particle size, and freely flowing. Mixed particle sized powders can segregate during manufacturing operations due to different densities, which can result in tablets with poor drug or active pharmaceutical ingredient (API) content uniformity but granulation should prevent this. Content uniformity ensures that the same API dose is delivered with each tablet.

Some APIs may be tabletted as pure substances, but this is rarely the case; most formulations include excipients. Normally, an pharmacologically inactive ingredient (excipient) termed a binder is added to help hold the tablet together and give it strength. A wide variety of binders may be used, some common ones including lactose, dibasic calcium phosphate, sucrose, corn, maize, starch, microcrystalline cellulose and modified cellulose (for eg. hydroxypropyl methylcellulose). Often, an

ingredient is also needed to act as a disintegrant to aid tablet disperssion once swallowed, releasing the API for absorption. Some binders, such as starch and cellulose, are also excellent disintegrants.

Small amounts of lubricants are usually added, as well. The most common of these is magnesium stearate; however, other commonly used tablet lubricants include stearic acid, stearin, hydrogenated oil, and sodium stearyl fumarate. These help the tablets, once pressed, to be more easily ejected from the die.

**Properties of an ideal tablet:**

The objective of formulation and fabrication of tablet is to deliver the correct amount of drug in proper form at or over proper time.

- Tablet should be elegant having its own identity and free from defects such as cracks, chips, contamination, discoloration etc.
- It should have chemical and physical stability to maintain its physical integrity over time.
- It should be capable to prevent any alteration in the chemical and physical properties of medicinal agent(s).
- It should be capable of withstanding the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing.
- An ideal tablet should be able to release the medicament(s) in body in predictable and reproducible manner.

**Advantages:**

- Tablets are unit dosage forms that provide an accurate, stable dose with greatest precision and least content variability.
- Tablets are easy to use, handle and carry by the patient.

- Tablets are attractive and elegant in appearance.
- Tablets are the most stable dosage form with respect to their physical, chemical and microbiological attributes.
- The manufacturing cost of tablets is low as compared to other dosage form and their manufacturing speed is also quite high.
- The packaging and shipping of tablets is comparatively easy and cheap.
- The unpleasant taste and odour of medicament(s) can be easily masked by sugar coating.
- The incompatibilities of medicament(s) and their deterioration due to environmental factors are less in case of tablet.
- Whenever a fractional dose is required, tablets are divided into halves and quarters by drawing lines during manufacturing to facilitate breakage.
- They are more suitable for large scale production than other oral dosage forms.
- Tablets provide administration of even minute dose of drug in an accurate amount.
- Their identification is probably the easiest because of variety of shapes and colors.
- Tablets are formulated with certain special release profile products such as enteric or delayed release products.

**Disadvantages:**

- Drugs that are amorphous in nature or have low density character are difficult to compress into tablet.
- Hygroscopic drugs are not suitable candidate for compressed tablets.
- Drugs having poor wetting properties, slow dissolution profile and high optimal gastro intestinal absorption are difficult or impossible to formulate as a tablet.
- Drugs having bitter taste and objectionable odour requires special treatment like coating or encapsulation which may increase their production cost.
- Drugs that are sensitive to oxygen or may also require certain treatment like special coating as well as packaging which may increase the overall manufacturing cost.
- High dose drugs are difficult to formulate as tablet dosage form.
- Some drugs which preferably get absorbed from the upper part of GIT may cause bioavailability problem in tablet dosage form.
- Drugs that are liquid in nature are difficult to formulate as a tablet.
- Swallowing of tablets especially by children and critically ill patients is very difficult.

**Tablet properties:**

Tablets can be made in virtually any shape, although requirements of patients and tabletting machines mean that most are round, oval or capsule shaped. More unusual shapes have been manufactured but patients find these harder to swallow, and they are more vulnerable to chipping or manufacturing problems. Tablet diameter and shape

are determined by the machine tooling used to produce them - a die plus an upper and a lower punch are required. This is called a station of tooling. The thickness is determined by the amount of tablet material and the position of the punches in relation to each other during compression. Once this is done, we can measure the corresponding pressure applied during compression. The shorter the distance between the punches, thickness, the greater the pressure applied during compression and sometimes the harder the tablet. Tablets need to be hard enough that they don't break up in the bottle, yet friable enough that they disintegrate in the gastric tract.

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall. Common minerals like talc or silica, and fats, eg. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.

**TYPES OF TABLETS:**

Tablets are classified according to their route of administration or function. The following are the 4 main classification groups:

**1. Tablets ingested orally**

a) Compressed tablets

b) Multiple compressed tablets

c) Multi layered tablets

d) Sustained action tablets

e) Enteric coated tablets

f) Sugar coated tablets

g) Film coated tablets

h) Chewable tablets

**2. Tablets used in the oral cavity, Buccal tablets**

a) Sublingual tablets

b) Lozenge tablets and torches

c) Dental cones

**3. Tablets administered by other routes**

a) Implantation tablets

b) Vaginal tablets

**4. Tablets used to prepare solutions**

a) Effervescent tablets, Molded tablets or tablet triturates (TT)

b) Dispersible tablets (DT)

c) Hypodermic tablets (HT)

**Compressed tablets:**

These tablets are uncoated and made by compression of granules. These tablets are usually intended to provide rapid disintegration and drug release. These tablets contain water-soluble drugs, which after swallowing get disintegrated in the stomach, and its drug contents are absorbed in the gastrointestinal tract and distribute in the whole body.

**Multiple compressed tablets:**

These tablets are prepared to separate physically or chemically incompatible ingredients or to produce repeated action, prolonged action products. To avoid incompatibility, the ingredients of the formulation except the incompatible materials

are compressed in to a tablet then incompatible substances along with necessary excipients are compressed in to a tablet.

**Multi layered tablets:**

These tablets consists of two or more layers of materials compressed successively in the same tablets. The color of each layer may be the same or different. The tablets having layers of different colors are known as "multicolored tablets".

**Method of preparation of granules and tablets: [Aulton M.E, 2007]**

The manufacture of granulation for tablet compression may follow one or a combination of 3 established methods:

**Direct compression:**

In direct compression method the raw materials are size reduced and the required excipients are added and directly compressed. A few crystalline substances can be directly compressed into tablets. Tablet development of lower strength drugs may follow two processes either by traditional alcoholic or aqueous wet granulation technique or via the simple direct compression mode with marginally faster dissolution rates. Dosage strength with 1-10 mg per 100 or 150 mg tablet is considered suitable drug candidates for direct compression.

**Advantages:**

- Low labour input.
- A dry process- advantage for those drugs, which degrade in moist conditions.
- Fewer processing steps- leading reduced cost.
- Direct compression dry blends are generally superior in dissolution than the equivalent wet granulation preparation incorporating up to 4% of super disintegrates.

**Disadvantages:**

- Differences in the particle size and bulk density between the drug and diluents may lead to stratification within the granulation and leads to content non uniformity.
- Direct compression diluents may interact with the drugs.
- It's not suitable for large dose drugs.
- Because of dry nature of the process, static charge may develop during the processes of screening and mixing.

**Main Steps Involved in the direct compression method is:**

Milling of drugs and excipients

↓

Mixing

↓

Tablet compression

**Wet granulation:**

This is most widely used and the most general method of the tablet preparation. Its popularity is due to the greater possibility that granules will meet all physical requirements for the compression of good tablets. Most powders cannot be compressed directly into tablets because the lack of proper characteristics of binding or together into a compact entity. The donor processes ordinarily lubricated and disintegrating properties. Wet granulation is the process in which the liquid is added to powder equipped with any type of agitation that will produce agglomeration or granules.

**Advantages:**

- The drugs having high dosage cohesiveness and compressibility of powder is improved due to the added binder that coats the individual powder particles, causing them adhere to each other so they can be formed into agglomerates called granules. During compaction process granules are fractured exposing fresh powder surface, which improves the compressibility.

- Lower pressures are needed to compress tablets results in improving tool life.

- Using wet method to obtain suitable flow and compression for cohesion must granulate drugs having high dosage and poor flow.

- Good distribution and uniform content for soluble, low dosage drugs and color additives are obtained if they are dissolved in binder solution.

- Bulky and dusty powders can be handled with out producing a great deal of dust and air borne contamination.

- Controlled release dosage forms can be accomplished by selection of suitable binder and solvent.

**Limitations:**

- Because of large number of processing steps, it requires a large area with temperature and humidity control.

- It requires a number of pieces of expensive equipment.

- Greater possibility of material loss during processing due to transfer of material from one unit operation to the other. Time consuming, especially in wetting drying steps.

**Main Steps involved in the Wet granulation method is:**

Sifting of Drugs and Excipients

↓

Mixing of Milled Powders.

↓

Preparation of Binder Solution.

↓

Mixing of Binder Solution with powder mixer to form wet mass then drying of Moist Granules

↓

Screening Dry Granules with Lubricant and Disintegrants

↓

Mixing of Screened Granules with Disintegrants and Lubricants for tablet compression

**Dry granulation:**

It is a valuable technique in situations where the effective dose of a drug is too high for direct compaction, and the drug is sensitive to heat, moisture, or both, which precludes wet granulation. This method involves the compaction of the components of a tablet formulation by means of a tablet press or specially designed machinery, followed by milling and screening, prior to final compression into tablet. When the initial blend of powders is forced into dies of large capacity tablet press and is compacted by means of flat faced punches, the compacted masses are called “slugs” and the process is referred to as “slugging”. On a large scale, “compression granulation”.

**Main Steps Involved in the Dry granulation method is:**

Milling of Drugs and Excipients

↓

Mixing of Milled Powders.

↓

Compression into large, hard tablets called slugs

↓

Screening of slugs

↓

Mixing with lubricant and disintegrating agent

↓

Tablet Compression.

**Excipients used in tablet formulation: [Lachmann and Libermenn, 2005]**

Excipient means any component other than the active pharmaceutical ingredient(s) intentionally added to the formulation of a dosage form. Many guidelines exist to aid in selection of nontoxic excipients such as IIG (Inactive Ingredient Guide), GRAS (Generally Regarded as Safe), Handbook of Pharmaceutical Excipients and others. While selecting excipients for any formulation following things should be considered wherever possible:

keep the excipients to a minimum in number, minimize the quantity of each excipient and multifunctional excipients may be given preference over unifunctional excipients. Excipients play a crucial role in design of the delivery system, determining its quality and performance. Excipients though usually regarded as nontoxic there are examples of known excipient induced toxicities which include renal failure and death from diethylene glycol, osmotic diarrhoea caused by ingested mannitol, hypersensitivity reactions from lanolin and cardiotoxicity induced by propylene glycol.

**Tablet excipients must meet certain criteria in formulation as follows:**

- They must be physiologically inert.
- They must be acceptable to regulatory agencies.
- They must be physically and chemically stable by themselves and in combination with the drugs and other tablet component.
- They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
- They must not interfere with the bioavailability of the drug.
- They must be commercially available in form and purity commensurate to pharmaceutical standards.
- For drug products that are classified as food, such as vitamins, other dietary aids, and so on, the excipients must be approved as food additives.
- Cost must be relatively inexpensive.
- They must be non-toxic.
- They must be commercially available in an acceptable grade in all countries where the product is to be manufactured.
- They must not be contra-indicated by themselves eg. sucrose, or because of a component eg. sodium, in any segment of the population.
- They must be color compatible, not produce any off color appearance.
- They must have no deterious effect on the bioavailability of the drug in the product.

**Binding agents:**

Binding agents play an important role in the manufacturing of tablets. Binding agents are also called as disintegrating agents. Binders are the glue that holds powder together to form granules. They are the adhesives that are added to tablet formulations to provide the cohesiveness required for the bonding together of the granules under compaction to form a tablet. The quantity used and the method of application must be carefully regulated, Since the tablet must remain intact until swallowed and must then release its medicament.

**Types of binding agents:**

**Binders are either sugars or polymeric materials. The later fall into two classes:**

- Natural polymers: starches, or gums including acacia, tragacanth & gelatin.
- Synthetic polymers: polyvinylpyrrolidone, methyl and ethyl cellulose, hydroxy propyl cellulose & povidone.

**Applications:**

- Wet binders: These are dissolved in a solvent (for eg. water or alcohol) and used in wet granulation process.

  Ex: gelatin, cellulose, cellulose derivatives, PVP, starch, sucrose, PEG

- Dry binders: These are added to the powder blend, either after a wet granulation Step, or as part of a direct powder compression formula.

  Ex: cellulose, methylcellulose, PVP, PEG.

**Lubricants:**

Lubricants are used in tablet formulation to ease the ejection of the tablet from the die to prevent sticking of tablets to the punches and to prevent excessive wear on punches and dies. They function by interposing a film of lower shear strength at the interface

between the tablet and the die wall and the punch face. Lubricant should be carefully selected for efficiency and for the properties of the tablet formulations.

**Classification of Lubricants:**

Lubricants are classified according to their water solubility i.e. water insoluble and water soluble. Selection of lubricant depends partly on mode of administration, type of tablet, desired disintegration and dissolution properties, physicochemical properties of granules or powder and cost.

**Water Soluble Lubricants:**

Water Soluble Lubricants are used when a tablet is completely soluble or when unique disintegration and dissolution characteristics are required. Tablet containing soluble lubricant shows higher dissolution rate than tablet with insoluble lubricants. Physical mixture of this lubricant i.e. SLS or MLS with stearates can lead to the best compromise in terms of lubricity, tablet strength and disintegration.

**Water Insoluble Lubricants:**

Water insoluble lubricants are most effective and used at reduced concentration than water soluble lubricants. Since these lubricants function by coating, their effectiveness is related with their surface area, extent of particle size reduction, time and procedure of addition and length of mixing.

**Disintegrants:**

Disintegrants constitute a group of materials that, on contact with water, swell, hydrate, change in volume or form, or react chemically to produce a disruptive change in the tablet. Disintegrant is the term applied to various agents added to tablet granulation for the purpose of causing the compressed tablet to break apart [disintegrate] when placed in an aqueous environment. The major function of disintegrants is to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet.

The stronger the binder, the more effective must be the disintegrating agent in order for the tablet to release its medication.

Ex: croscaramellose sodium, crospovidone, sodium starch glycolate.

**METHOD OF ADDITION OF DISINTEGRANTS**:

The requirement placed on the tablet disintegration should be clearly defined. The ideal disintegrant has,

- Poor solubility.
- Poor gel formation.
- Good hydration capacity.
- Good molding and flow properties.
- No tendency to form complexes.

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment.

**There are 2 methods used for incorporating disintegrating agents into tablets.**

**Method 1: one-step method:**

This method involves:

- External addition
- Internal addition

In external addition, the disintegrant is added to the sized granulation with mixing just prior to compression in internal addition. The disintegrants is mixed with other powder before wetting the powder mixture with the granulating solution. Thus the disintegrants is incorporated with the granule.

**Method 2: Two-step method:**

In this method, a part of the disintegrant can be added internally and a part externally. This provides immediate disruption of the tablet into the previously compressed granules which the disintegrating agent with in the granules process further erosion of the granules to the original powder particles. Although this latter is an attractive theory, it is only partially effective in practice because any disintegrating agent bound with in the granules loses some of the disruptive force due to its encasement by the binder. Nevertheless, the 2-step method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

**Super disintegrants in immediate release tablets:**

A disintegrant is an excipient which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment. This is especially important for immediate release products where rapid release of drug substance is required. A disintegrant can be added to a powder blend for direct compression or encapsulation. It can also be used with products that are wet granulated. While there are some tablets fillers (starch, MCC) which aid in disintegration, there are more effective agents referred to as superdisintegrants.

Ex: croscarmelose, crospovidone, and sodium starch glycolate.

**Diluents:**

Diluents are fillers comprise a heterogeneous group of substances, designed to makeup the required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk. The dose of some drugs is sufficiently high that no filler is required.

Ex: micro crystalline cellulose, lactose monohydrate, aspirin and certain antibiotics.

Tablet formulations may contain diluents for secondary reasons, to provide better tablet properties such as improved cohesion, to permit use of direct compression manufacturing, or to promote flow.

Antiadherents, some materials have strong adhesive properties towards the metal of punches and dies or the tablet formulation containing excessive moisture which has tendency to result in picking and sticking problem. Therefore Antiadherents are added, which prevent sticking to punches and die walls. Talc, magnesium stearate and corn starch have excellent Antiadherents properties. Vegan had suggested that silicon oil can be used as Antiadherents.

**Glidants:**

Glidants are materials that improve the flow characteristics of granules by reducing the inter particulate friction. In proper amounts they also serve to assure smooth and uniform flow at all times. Glidants are useful in tablet formulations to attain free flow of granules, to permit use of direct compression or wet granulation for manufacturing process. Glidants give better control over the flow of the powder mixtures used to produce tablets and capsules with uniform and consistent flow.

Ex: magnesium stearate, colloidal silicon dioxide, starch and talc.

**IMMEDIATE RELEASE DRUG DELIVERY SYSTEM: [LoydAllen V, 1999]**

Immediate release drug delivery system is also conventional type of drug delivery system and it is defined as - Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques.

**Advantages of immediate release drug delivery systems:**

- Release the drug immediately.
- More flexibility for adjusting the dose.

- It can be prepared with minimum dose of drug.
- There is no dose dumping problem.
- Immediate release drug delivery systems used in both initial stage and final stage of disease.

Immediate release tablets (conventional tablets): The tablet is intended to be released rapidly after administration or the tablet is dissolved and administered as solution. It is the most common type and includes:

- Orally disintegrating tablet
- Sublingual tablet
- Chewable tablet
- Buccal tablet
- Effervescent tablet

**Orally disintegrating tablets:**

Orally disintegrating tablets (ODT) are solid dosage forms that disintegrate in the oral cavity leaving an easy-to-swallow residue. The disintegration times are generally less than one minute. For orally disintegrating tablets, taste-masking of bitter or objectionably-tasting drug substances is critical. The taste-masking aspect plays a significant role in dissolution method development, specifications, and testing. The USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets. Discriminating, robust dissolution methods are extremely useful for monitoring process optimization and changes during scale-up of taste-masked bulk drug and tablet manufacture.

**Sublingual Tablets:**

Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where polatable liquids are not available. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes.

**Chewable tablets:**

The patients who have difficulty in swallowing tablets whole or for children who have not yet learnt to swallow a tablet, chewable tablet serves as an attractive alternative. The added advantage of this medication is that it can be taken at any time or when water is not available. Mannitol is normally used as a base due to low hygroscopy and more importantly, it gives pleasant, cooling sensation. Antacid tablets are invariably prepared as chewable to obtain quick ingestion relief as well as the antacid dose is too large to swallow and the activity is related to particle size. Another example is multivitamin tablet which a patient can take as a daily dose.

Many of the excipients commonly used in tablet formulations are especially applicable for use in chewable tablets due to their ability to provide the necessary properties of sweetness and chewabilty. In general these fall into the sugar category, although a combination of excipients with artificial sweeteners may provide a satisfactory alternative.

Uko-Nne and Mendes reported on the development of dried honey and molasses products marketed for use in chewable tablets. Both are free-flowing compressible materials with characteristics colours, odours and tastes that limit their primary applicability to the vitamin/food supplement field.

**Buccal tablets:**

Tablets designed to dissolve on the buccal (cheek) mucous membrane were a precursor to the ODT. This dosage form was intended for drugs that yield low bioavailability through the digestive tract but are inconvenient to administer parenterally, such as steroids and narcotic analgesics. Absorption through the cheek allows the drug to bypass the digestive tract for rapid systemic distribution. Not all ODTs have buccal absorption and many have similar absorption and bioavailability to standard oral dosage forms with the primary route remaining GI absorption. However, a fast disintegration time and a small tablet weight can enhance absorption in the buccal area. The first ODTs disintegrated through effervescence rather than dissolution, and were designed to make taking vitamins more pleasant for children. This method was adapted to pharmaceutical use with the invention of microparticles containing a drug, which would be released upon effervescence of the tablet and swallowed by the patient.

**Effervescent tablets:**

Effervescent or Carbon tablets are tablets which are designed to break in contact with water or another liquid, releasing carbon dioxide in the process. Rapid break down often may cause the tablet to dissolve in to a solution, and is also often followed by a froth. These kind of tablets are usually used to deliver drugs or to encapsulate cleaning products, such as the enzymatic cleaners designed for wetsuits.

These tablets are products of compression of component ingredients in to a dense mass, which is packaged in an airtight container or a blister pack. When is necessary, people can drop them in to water or another liquid to make a solution. Cleaning tablets may be added to filled tubs of water, depending on the packaging directions.

From a drug delivery perspective, there are several advantages to effervescent tablets. One of the biggest advantage is that they deliver drugs to the body rapidly, because the drug is delivered in the form of a solution that is easy to absorb. Dosage control also is easier, and effervescent tablets can be used to protect certain ingredients from the highly acidic environment of the stomach.

**DISEASE PROFILE:**

**Blood Pressure:**

Blood pressure is the force of blood against the walls of arteries. Blood pressure is recorded as two numbers-the systolic pressure (as the heart beats) over the diastolic pressure (as the heart relaxes between beats). The measurement is written one above or before the other, with the systolic number on top and the diastolic number on the bottom. For example, a blood pressure measurement of 120/80 mmHg (millimeters of mercury) is expressed verbally as "120 over 80."

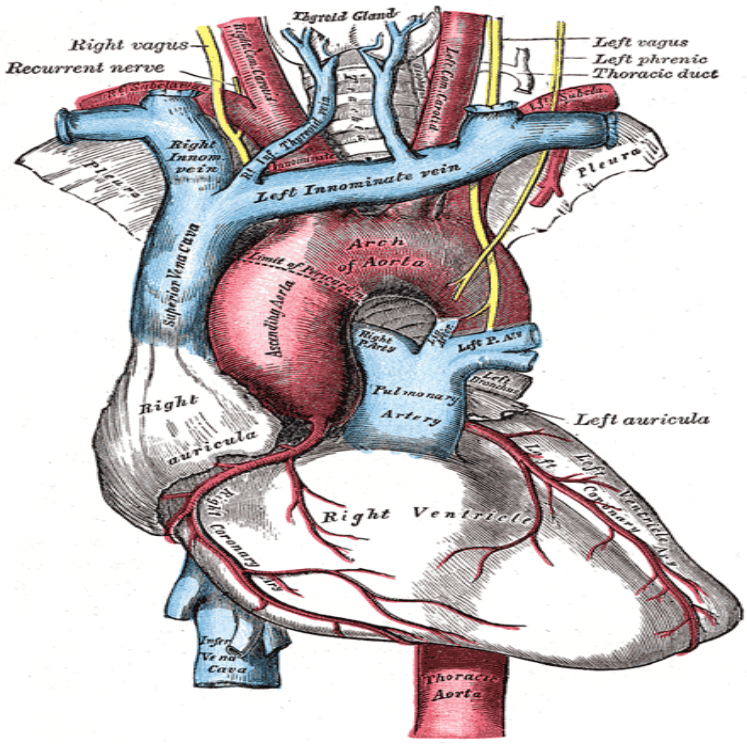



**Fig.1: The arch of the aorta (main artery exiting the heart) and its branches**

**Table. 1: Classification of Blood pressure**

| CONDITION | Systolic pressure | | Diastolic pressure | |
|---|---|---|---|---|
| | **mmHg** | **kPa** | **mmHg** | **kPa** |
| Normal | 90-119 | 12-15.9 | 60-79 | 8.0-10.5 |
| Pre-hypertension | 120-139 | 16.0-18.5 | 80-89 | 10.7-11.9 |
| Stage 1 | 140-159 | 18.7-21.2 | 90-99 | 12.0-13.2 |
| Stage 2 | ≥160 | ≥21.3 | ≥100 | ≥13.3 |
| Isolated systolic hypertension | ≥140 | ≥18.7 | <99 | <12.0 |

Blood pressure is usually classified based on the systolic and diastolic blood pressures. Systolic blood pressure is the blood pressure in vessels during a heart beat. Diastolic blood pressure is the pressure between heartbeats. A systolic or the diastolic blood pressure measurement higher than the accepted normal values for the age of the individual is classified as pre-hypertension or hypertension.

Hypertension has several sub-classifications including, hypertension stage I, hypertension stage II, and isolated systolic hypertension. Isolated systolic hypertension refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly.

**Causes**

**Essential hypertension:**

Essential hypertension is the most prevalent hypertension type, affecting 90-95% of hypertensive patients. Although no direct cause has identified itself, there are many factors such as sedentary lifestyle, smoking, stress, visceral obesity, potassium deficiency (hypokalemia) obesity (more than 85% of cases occur in those with a body mass index greater than 25), salt (sodium) sensitivity, alcohol intake, and vitamin D deficiency that increase the risk of developing hypertension. Risk also increases with

aging, some inherited mutations, and having a family history of hypertension. An elevation of renin, a hormone secreted by the kidney, is another risk factor.

**Secondary hypertension:**

Secondary hypertension by definition results from an identifiable cause. This type is important to recognize since it's treated differently to essential hypertension, by treating the underlying cause of the elevated blood pressure. Hypertension results in the compromise or imbalance of the path physiological mechanisms, such as the hormone-regulating endocrine system, that regulate blood plasma volume and heart function. Many conditions cause hypertension, some are common and well recognized secondary causes such as Cushing's syndrome, which is a condition where the adrenal glands overproduce the hormone cortisol.

**Prevention:**

- Weight reduction and regular aerobic exercise (eg. walking): Regular exercise improves blood flow and helps to reduce the resting heart rate and blood pressure.

- Reducing dietary sugar.

- Reducing sodium (salt) in the diet: This step decreases blood pressure, many people use a salt substitute to reduce their salt intake.

- Additional dietary changes beneficial to reducing blood pressure include the DASH diet (dietary approaches to stop hypertension) which is rich in fruits and vegetables and low-fat or fat-free dairy products. This diet has been shown to be effective based on research sponsored by the National Heart, Lung, and Blood Institute. In addition, an increase in dietary potassium, which offsets the effect of sodium has been shown to be highly effective in reducing blood pressure.

- Discontinuing tobacco use and alcohol consumption has been shown to lower blood pressure.

**Treatment**

**Lifestyle modifications:**

The first line of treatment for hypertension is the same as the recommended preventative lifestyle changes such as the dietary changes, physical exercise, and weight loss, which have all been shown to significantly reduce blood pressure in people with hypertension.

**Medications:**

Several classes of medications, collectively referred to as antihypertensive drugs, are currently available for treating hypertension. Agents within a particular class generally share a similar pharmacological mechanism of action, and in many cases have an affinity for similar cellular receptors. An exception to this rule is the diuretics, which are grouped together for the sake of simplicity but actually exert their effects by a number of different mechanisms. Often multiple drugs are combined to achieve the goal blood pressure. Commonly used prescription drugs include:

- ACE inhibitors (eg. captopril)
- Alpha blockers (eg. prazosin)
- Angiotensin II receptor antagonists (eg. losartan)
- Beta blockers (eg. propranolol)
- Calcium channel blockers (eg. verapamil)
- Diuretics (eg. hydrochlorothiazide)
- Direct renin inhibitors (eg. aliskiren)

Some examples of common combined prescription drug treatments include:

- A fixed combination of an ACE inhibitor and a calcium channel blocker. One example of this is the combination of perindopril and amlodipine, the efficacy of which has been demonstrated in individuals with glucose intolerance or metabolic syndrome.

- A fixed combination of an ACE inhibitor and a calcium channel blocker.

- A fixed combination of a diuretic and an ARE.

Combinations of an ACE inhibitor or angiotensin II-receptor antagonist, a diuretic and an NSAID (including selective COX-2 inhibitors and non-prescribed drugs such as ibuprofen) should be avoided whenever possible due to a high documented risk of acute renal failure. The combination is known as a "triple whammy" in the Australian health industry.

In the present study Olmesartan medoxomil was choosed to develop immediate release tablets for treatment of hypertension.

# REVIEW OF LITERATURE

**Rathnanand, et al, (2011).,** Prepared and evaluated (*in vitro)* nizatidine immediate release tablets. The developed drug delivery system delivers a programmed dose of drug intended for excessively secreted gastric acid and for promoting healing of duodenal ulcers thereby spontaneously delivering the drug when exposed into GIT for producing an anti-ulcer effect. Accordingly, immediate release drug-containing core tablets of Nizatidine were prepared by wet granulation method. The obtained tablets were evaluated for weight variation, thickness, hardness, drug content, disintegration and *in vitro* dissolution studies. Stability studies of the optimized formulation was carried out as per ICH guidelines at 40 ± $2^{o}$C / 75 ±5% RH for one month and it was found to be stable.

**Sivasakthi, et al, (2011).,** Observed that reverse phase-high performance Liquid chromatography method is a simple, accurate, precise and reproducible one. UV-Spectrophotometric simultaneous equation method is adopted by official compendia for the stable substance that have reasonably broad absorption bands and which are practically unaffected by the variations of Instrumental parameters. A reverse phase high performance liquid chromatography method has been developed for the simultaneous estimation of Olmesartan medoxomil and Hydrochlorthiazide acid in tablet dosage form. The method was linear over the concentration range for Olmesartan medoxomil 5-70µg/ml and for Hydrochlorthiazide 5–50µg/ml. The mean recovery was found to be in the range of 98% to 102%. The Validation method was carried out using International Conference on Hormonisation Guidelines. The described RP-HPLC method was successfully employed for the analysis of Pharmaceutical formulations containing combined dosage form.

**Tiwari A.K, et al, (2011).,** Prepared and evaluated the immediate release tablet of Drotaverine HCL by Wet granulation method, the method has very high flow of powder blend that might create the problem of uneven dye filling. The Superdisintegrant AC-Di-Sol and Crospovidone were used for immediate release of drug from tablet. The coating was done to minimize the oxidation of Drotaverine

HCL. From the results, it can be concluded that increase in concentration of superdisintegrant will lead to decrease the disintegration time up to 8 min after coating without any change observed in the dissolution profile of drug.

**Vaishnani, et al, (2011).,** Prepared various formulations of immediate release tablet of paroxetine using different superdisintegrants (sodium starch glycolate, croscarmellose, crospovidone)by wet granulation method. It is a selective serotonin reuptake inhibitor(SSRI) used in treatment of depression. Paroxetine have become first line drug in the pharmacotherapy of patients with depression. This is because the drug possesses tolerability and safety advantages over the tricyclic agents. Their results were found satisfactory. The invitro dissolution studies shows the release is in the following order of superdisintegrants: sodium starch glycolate > croscarmellose > crospovidone.

**Klaus O. Stumpe MD, et al, (2010).,** Compared the antihypertensive efficacy of olmesartan with that of 4 other AURAS, at recommended maintenance doses, already in clinical use for the treatment of hypertension, the doses studied. These differences in blood pressure reduction between these agents may be clinically relevant and have important long-term implications. Additional studies will further define the role of olmesartan in the management of cardiovascular diseases, such as atherosclerosis.

**Mallion JM, et al, (2010).,** Compared the efficacy and safety of olmesartan medoxomil (O) and ramipril (R) in elderly patients with essential arterial hypertension and concluded that in elderly patients with essential arterial hypertension, olmesartan provides an effective, prolonged and well tolerated blood pressure control with significantly better blood pressure normalization than ramipril and represents a useful option among first-line drug treatments of hypertension in this age group.

**Mire, et al**, **(2010).,** Studied on angiotensin II ($AT_1$) type 1 ($AT_1$) receptor-mediated effects of A-IT play a key role in the pathophysiology of hypertension. Effective inhibition of A-IT is provided by the latest class of antihypertensive medications, the $AT_1$ receptor blockers (ARBs). These orally available agents were developed around a common imidazole-based structural core. After oral administration, olmesartan

medoxomil is de-esterified in the intestinal tract to produce the active metabolite olmesartan, which undergoes no additional metabolic change. The marked antihypertensive efficacy of olmesartan medoxomil may result from a unique pharmacological interaction of the drug with the AT1 receptor, resulting in a potent, long-lasting, dose-dependent blockade of A-IT.

**Miyoshi T, et al, (2010).,** Evaluated the effects of angiotensin II type 1 receptor blocker (ARB) on arterial stiffness and its association with serum A-FABP in patients with hypertension. Thirty patients newly diagnosed with essential hypertension were treated with olmesartan (20mg/day), an ARB, for 6 months. Olmesartan treatment resulted in a significant decrease in CAVI, serum A-FABP levels, and hsCRP, besides a significant reduction of blood pressure. Olmesartan ameliorated arterial stiffness in patients with hypertension, which may be involved in the reduction of serum A-FABP.

**Parambi, et al, (2010).,** A simple, rapid, economical, accurate and precise method has been developed for estimation of Olmesartan medoxomil from tablet dosage form. The absorption maxima in THF solvent was found to be 265nm and Beer's law was obeyed in a concentration range of 5-30mcg/ml and coefficient of correlation for Olmesartan was found to be 0.9997.The precisional accuracy of the developed method were confirmed by repeatability and recovery studies are validated statistically. The limit of detection and limit of quantitation of Olmesartan were found to be 0.23mcg/ml and 0.77mcg/ml respectively. The percentage recovery was found to be 99.37% for Olmesartan. The method showed good repeatability and recovery with relative standard deviation less than 2. So, this developed method can be used for the routine analysis of Olmesartan medoximil from formulations.

**Parikh B.N, et al, (2010).,** Developed solid oral formulations of Telmisartan which can be prepared for long-lasting stability of the formulation under different climatic conditions and sufficient solubility of the active substance for sufficient gastrointestinal absorption in the slightly acidic and neutral pH region. Preferably, the formulations should have immediate release characteristics and a dissolution showing no essential pH dependency within the physiological relevant pH interval of the

gastrointestinal tract. Tablets were evaluated for various parameters like, weight variation, content uniformity, in-vitro dissolution studies were performed using United States Pharmacopeia (USP) apparatus type II. The effects of concentration of meglumine, povidone and different alkalizers on the release rate of Telmisartan were studied. Telmisartan has poor and pH dependent water solubility in order to enhance its dissolution different alkalizers were used and concluded that, significantly increased the drug dissolution rate in intestinal stimulated fluid (pH 7.5), slightly acidic (pH 1.2) and water.

**Punzi H, et al, (2010).,** studied the use of ambulatory blood pressure (BP) monitoring (ABPM) to determine the efficacy of a fixed-dose combination of amlodipine (AML) and olmesartan medoxomil (OM) over the 24-hour dosing interval. This 12-week, titrate-to-goal study was conducted in 185 patients with hypertension. Patients were initially treated with AML 5 mg/day and up titrated to AML/OM 5/20, 5/40, and 10/40 mg/day every 3 weeks if mean seated BP (SeBP) was >/=120/80 mmHg. An AML/OM-based titration regimen effectively reduces BP in patients with hypertension.

**Rana R, et al, (2010).,** Found that Olmesartan medoxomil 20 mg once daily is not only effective in achieving the desired BP in a significant number of patients, it also shows excellent tolerability and hence compliance. Olmesartan is a valuable option for treatment of essential hypertension in adult patients.

**Rump LC, et al, (2010).,** Observed that cardiovascular disease is a major cause of premature death and disability worldwide, and effective blood pressure (BP) control is crucial for the reduction of cardiovascular risk in patients with hypertension. Despite this, many will fail to attain recommended BP goals. A reappraisal of European guidelines led to revised recommendations for BP reduction to values with in the SBP/DBP range of 130-139/80-85 mmHg in all patients with hypertension, including higher-risk groups such as those with diabetes.

**Rump LC, et al, (2010).,** Observed that high dose (40mg) olmesartan medoxomil (OM) blocks the angiotensin II receptor, significantly reducing blood pressure (BP).

Adding hydrochlorothiazide (HCTZ) to OM increases efficacy. Adding HCTZ to OM 40mg significantly improves BP reductions and target BP rates in harder to treat patients and a clear dose-response was observed for efficacy.

**Tatsuya Suzuki, et al, (2010).,** Performed dissolution test for the acetaminophen-MCC (10:90) tablets. Dissolution profiles showed an interesting phenomenon, namely the dissolution rate of acetaminophen from MCC tablet decreased when the degree of crystallinity of MCC was in the range from 65.5 to 37.6%, however, it increased markedly when the degree of crystallinity of MCC was in the range from 25.8 to 12.1%. The amount of water absorbed into tablets changed in accord with the dissolution rates of acetaminophen from tablets. The dissolution data indicate that drug release can be modified by changing the degree of crystallinity of MCC.

**Wilford Germino F, et al, (2010).,** Worked and observed that angiotensin II receptor blockers (ARBs) are well tolerated and demonstrate significant BP reduction. Olmesartan medoxornil (OM), an ARB, has been well studied and achieves significant BP lowering and goal achievement with good tolerability. His review evaluates clinical efficacy and safety. Data from 5 OM-based studies: 4 dose-titration studies and 1 factorial study. Study results demonstrate that OM ± hydrochlorothiazide is highly effective in reducing BP while enabling a majority of patients with stage 1 hypertension to achieve BP goal.

**Choudhary D, et al, (2009).,** Explained that, because to the poor water solubility of the Glipizide, its bioavailability is dissolution rate-limited. The purpose of this study was is to increase the solubility of Glipizide (GZ) in aqueous media by solid dispersion (SDs) technique with Poloxamer (PXM) 188 and Poloxamer (PXM) 407 by using the kneading method No chemical interaction was found between GZ and PXM 188 or PXM 407 by the results of DSC. XRD and SEM studies show that PXM 188 or PXM 407 inhibits the crystallization of GZ. The SDs prepared in this study were found to have better dissolution rates in comparision compared to intact GZ and physical mixture of PXM 188 or PXM 407 and GZ. It was found that the optimum weight ratio for drug:Carrier is 1:5 for PXM 188 and l:6 for PXM 4O7.

**Durgacharan A Bhagwat, et al, (2009).,** Demonstrated effect of release enhancers such as microcrystalline cellulose (MCC) and lactose on in-vitro drug release was also studied in sustained release tablets of verapamil. The results showed that PREC can be utilized as the matrix forming agent to sustain the release of VPH. More bioavailability was noted with the sustained release formulation even though the drug has substantial first pass metabolism. The results indicated that it is possible to make once a day sustained release tablet of VPH by using the melt granulation technique.

**Rai V.K, et al, (2009).,** Prepared Raloxifene Hydrochloride immediate release tablets by wet granulation technique. In order to obtain the best, optimized product six different formulations were developed. Different filler, binder, disintegrant and lubricant were taken as variables. Weight variation, hardness, friability, disintegration time, in-vitro release and pharmaceutical assay were studied as response variables. Sticking was observed when the formulation containing stearic acid and sodium stearyl fumarate. How ever, in the remaing four formulations containing magnesium stearate, no sticking was observed. The different physical properties and in-vitro release profile showed best comparable with reference product.

**MallikarjunaSetty.C, et al, (2008).,** Prepared aceclofenac fast-dispersible tablets by direct compression method. Effect of superdisintegrants (such as, croscarmellose sodium, sodium starch glycolate and crospovidone) on wetting time, disintegration time, drug content, in vitro release and stability parameters has been studied. Disintegration time and dissolution parameters (t50% and t80%) decreased with increase in the level of croscarmellose sodium. Whereas, disintegration time and dissolution parameters increased with increase in the level of sodium starch glycolate in tablets. It is concluded that fast-dispersible aceclofenac tablets could be prepared by direct compression using superdisintegrants.

**Mukeshgohel, et al, (2004).,** Developed mouth dissolve tablets of nimesulide. Granules containing nimesulide, camphor, crospovidone, and lactose were prepared by wet granulation technique. Alternatively, tablets were first prepared percentage friability, wetting time, and disintegration time. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form,

tablets should be prepared using an optimum concentration of camphor and a higher percentage of crospovidone. The systematic formulation approach helped in understanding the effect of formulation processing variables.

**Perissutti, B, et al, (2003).,** Reported preparation of fast release dosage form for carbamazepine involving the use of melt granulation process in high shear mixer for production of tablets. Crospovidone was used as releasing agent. The results showed enhancement of dissolution with intragranular addition of crospovidone, while extra granular addition of crospovidone causes fast disintegration.

**Ferrero.C, et al, (1997).,** Investigated the efficiency of croscarmellose sodium (Ac-DiSol®) in a direct compression formulation containing a poorly water soluble drug (albumin tanate) at high dose. An experimental design with two variables, applied pressure and concentration of Ac-Di-Sol®, allowed the evaluation of disintegration properties of the tablets. Tablet properties evaluated were affected by both variables, while compression parameters were essentially dependent on applied pressure.

**Desai D.S, et al, (1996).,** Prepared combination wet granulated tablet formulation of an antihypertensive drug A and HCTZ containing povidone K-30 NF (PVP) as a binder and poloxamer 188 NF (Pluronic® F68) as a wetting agent. It was hypothesized that the mechanism of degradation of HCTZ in the presence of PVP and/or Pluronic® F68 was due to solubilization of the HCTZ by these excipients in the moisture present in tablets, followed by its hydrolysis.

**Van Kamp, et al, (1983).,** Studied about the improvement of tabletting properties of super disintegrants by wet granulation. The crushing strength, disintegration and dissolution properties of tablets, made by wet granulation with lactose as filler, gelatin as binder, potato starch as disintegrant and magnesium stearate as lubricant would be markedly improved when potato starch (20%) was replaced by much lower concentration (4%) of an insoluble super disintegrant, such as SSG or crospovidone.

# AIM AND OBJECTIVE OF THE WORK

**AIM:** The aim of this study is to formulate and develop immediate release tablet of olmesartan medoxomil.

**OBJECTIVE:** The objective of this study is to obviate the demerits of slow release and slow absorption of normal tablets of olmesartan and to get immediate effect of the drug in the treatment of hypertension.

To study the effect of super disintegrants on the release of olmesartan medoxomil. Different super disintegrants are used to attain immediate drug release and to give maximum therapeutic effect in short span of time when taken orally, finally to design a formulation of solid dosage form of olmesartan tablets with better stability of high product quality.

# PLAN OF WORK

The plan of the research work has been scheduled as:

I. API and excipients characterization to prepare solid oral dosage form of olmesartan.

II. Preformulation studies:

- Compatability studies
- Solubility
- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausners ratio
- Moisture content

III. Development of immediate release olmesartan tablets by wet granulation method.

IV. Evaluation of the formulated tablets for their physiochemical characteristics such as:

- Hardness
- Thickness
- Friability
- Weight variation
- Disintegration
- Content uniformity

V. *In-vitro* drug dissolution study of the prepared tablets of olmesartan medoxomil.

VI. Stability studies.

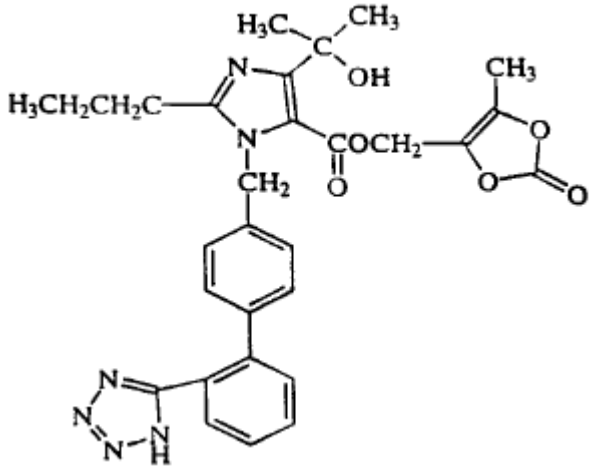
# DRUG PROFILE

**Chemical name** : Olmesartan medoxomil (Wilson and Gisvold's, 1998) is described chemically as 2,3-dihydroxy-2-butenyl 4(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole5-carboxylate, cyclic 2,3-carbonate.

**Empherical formula :** $C_{29}H_{30}N_6O_6$

**Molecular weight :** 558.59

**Structural formula :** The olmesartan molecule includes one tetrazole group (a 5- member heterocyclic ring of four nitrogen and one carbon atom) and one imidazole group (a 5-membered planar heterocyclic aromatic ring of two nitrogen and three carbon atoms, classified as an alkaloid).




**Description :** White to off-white crystalline powder

**Solubility :** It is freely soluble in chloroform and in glacial acetic acid, slightly soluble in methanol and in acetonitrile and practically insoluble in water, ethyl acetate and in n-hexane.

## CLINICAL PHARMACOLOGY

### Mechanism of action:

Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Olmesartan is a prodrug that works by blocking the binding of angiotensin II to the $AT_1$ receptors in vascular muscle; it is therefore independent of angiotensin II synthesis pathways. By blocking the binding rather than the synthesis of angiotensin II, olmesartan inhibits the negative regulatory feedback on renin secretion. As a result of this blockage, olmesartan reduces vasoconstriction and the secretion of aldosterone. This lowers blood pressure by producing vasodilation, and decreasing peripheral resistance.

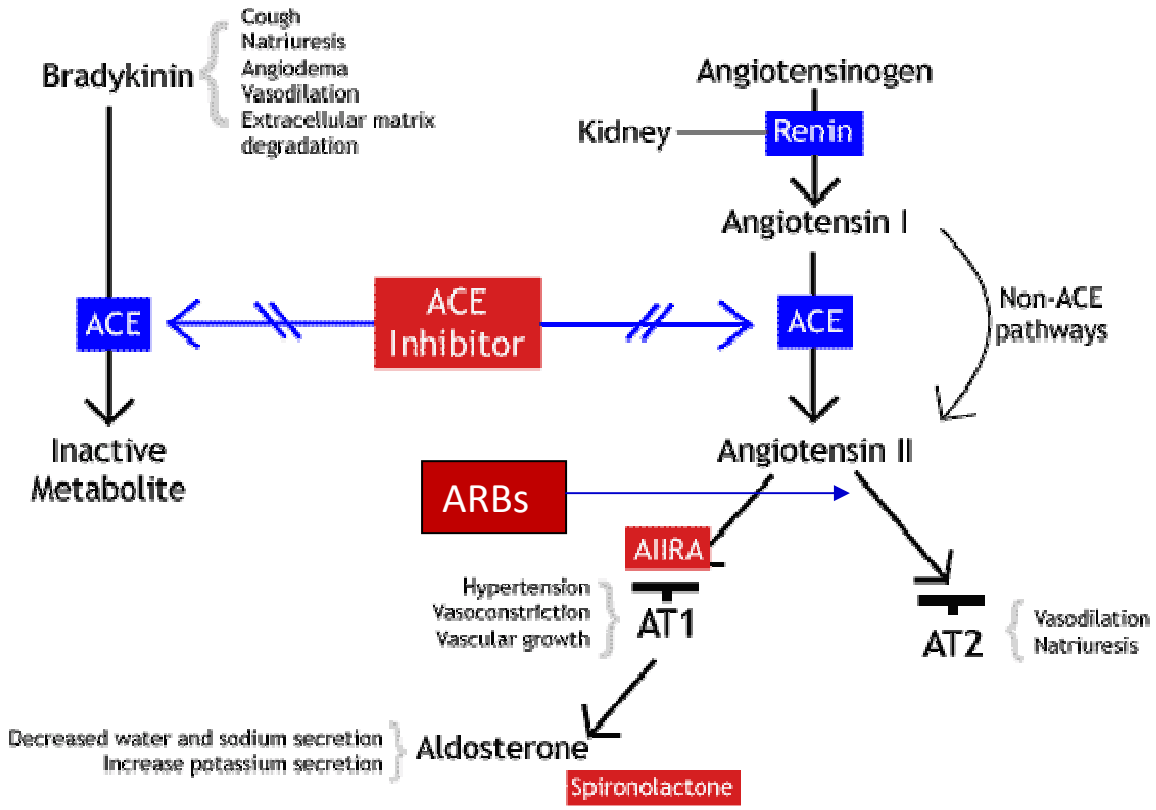



**Fig.2:** Renin-angiotension system showing site of action of angiotension converting enzyme inhibitors and angiotension II receptors blockers.

**Pharmacokinetics:**

**General:**

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective $AT_1$ subtype angiotensin II receptor antagonist. Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. The absolute bioavailability of olmesartan is approximately 26%. Food does not affect the bioavailability of olmesartan. After oral administration, the peak plasma concentration (Cmax) of olmesartan is reached after 1 to 2 hours.

**Metabolism and Excretion:**

Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.

**Distribution:**

The volume of distribution of olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses.

**Pharmacodynamic:**

Olmesartan medoxomil doses of 2.5 to 40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses of olmesartan medoxomil > 40 mg giving > 90% inhibition at 24 hours.

Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increase after single and repeated administration of olmesartan medoxomil to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg olmesartan medoxomil had minimal influence on aldosterone levels and no effect on serum potassium.

**Dosage and administration:**

Dosage must be individualized. The usual recommended starting dose of Benicar is 20mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose of Benicar may be increased to 40mg. Doses above 40mg do not appear to have greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily.

**Side effects:**

Back pain, bronchitis, creatine phosphokinase increased, diarrhoea, headache, haematuria, hyperglycemia, hypertriglyceridemia, influenza-like symptoms, pharyngitis, rhinitis and sinusitis.

**Storage:**

Store at 20-25°C (68-77°F).

# EXCIPIENTS PROFILE

Following excipients (Hand book of pharmaceutical excipients, 5th edition by Raymond C Rowe, 2005) are used in this wet granulation method.

## 1. LACTOSE MONOHYDRATE

**Synonyms:** Capsulac; granulac; lactochem; lactosum; monohydrate; pharmatose.

**Chemical name:** O-β-D – galactopyranosyl - (1→4) – α – D-glucopyranose monohydrate.

**Empherical formula:** $C_{12}H_{22}O_{11}.H_{20}$

**Functional category:** Dry powder capsule diluents; tablet and capsule filler; Inhaler carrier; lyophilisation aid; tablet binder.

**Applications in pharmaceutical formulations:** It is widely used as a filler and diluent in tablet and capsule and more limited extent in lipophilised products. Lactose is also used as a diluent in dry powder inhalations.

**Description:** In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose anhydrous, and stable α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

**Solubility:** Freely but slowly soluble in water, soluble in ethanol, insoluble in alcohol.

**Stability and storage conditions:** Mold growth may occur under humid conditions.

## 2. MICROCRYSTALLINE CELLULOSE

**Synonyms:** Avicel H; cellets; cellulose gel; hellulosum microcrystallinum.

**Chemical name:** Cellulose

**Empherical formula:** $(C_6H_{10}O_5)_n$

**Functional category:** Adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

**Applications in pharmaceutical formulations:** Microcrystalline cellulose is widely used in pharmaceuticals primarily as a binder/diluents in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes. In addition to its as a binder/diluents microcrystalline cellulose has some lubricant and disintegrant properties that make it useful in tabletting.

**Description:** Microcrystalline cellulose is a purified, partially depolymerised cellulose that occurs as white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grade different properties and applications.

**Solubility:** Slightly soluble in 5% w/v sodium hydroxide solution practically insoluble in water, dilute acids and most organic solvents

**Stability and storage conditions:** Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well closed container in a cool, dry place.

## 3. CROSCARMELLOSE SODIUM

**Synonym:** AC-DI-SOL; carmellosum notricum conexum; cross linked carboxy methyl cellulose sodium.

**Chemical name:** Cellulose, carboxy methyl ether, sodium salt.

**Functional category:** Tablet and capsule disintegrant.

**Empherical formula:** $C_{12}H_{10}Ca_3O_{14}.4H_2O$

**Applications in pharmaceutical formulations:** It is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules.

**Description:** Croscarmellose sodium occurs as an odourless, white or greyish white powder.

**Solubility:** Insoluble in water, although croscarmellose sodium rapidly swell to 4-8 times its original volume on contact with water. practically insoluble in acetone, ethanol and toluene.

**Stability and storage conditions:** Croscarmellose sodium is a stable through hygroscopic material.

A model tablet formulation prepared by direct compression, with croscarmellose sodim as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months. Croscarmellose sodium should be stored in a well closed container in a cool and dry place.

**4. MAGNESIUM STEARATE**

**Synonyms:** Dibasic magnesium stearate; magnesium di stearate; magnesium salt; steric acid.

**Chemical name:** Octadecanoic acid magnesium salt.

**Empherical formula:** $C_{36}H_{70}MgO_4$

**Functional category:** Tablet and capsule lubricant.

**Applications in pharmaceutical formulations:** Magnesium stearate is widely used in cosmetics, food and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentration between 0.25% and 5.0%w/w.

**Description:** Magnesium stearate is a very fine, light white, precipitated or milled, powder of low bulk density, having a faint odour of stearic acid and a characteristic taste .The powder is greasy to touch and readily adhere to the skin.

**Solubility:** Practically insoluble in ethanol (95%), ether and water, slightly soluble in warm benzene and ethanol.

**Stability and storage conditions:** Magnesium stearate is stable and should be stored in a well closed container in cool and dry place.

**5.CROSPOVIDONE**

**Synonyms:** Crosslinked povidone; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL 10; polyvinylpolypyrrolidone; 1-vinyl-2-pyrrolidinone homopolymer.

**Chemical name:** 1-Ethenyl-2-pyrrolidinone homopolymer

**Empherical formula:** (C6H9NO)n

**Functional category:** Tablet disintegrant.

**Applications in pharmaceutical formulations:** Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

**Description:** Crospovidone is a white to creamy-white, finely divided, freeflowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

**Solubility:** Practically insoluble in water, in alcohol, and in methylene chloride.

**Stability and storage conditions:** Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

**6. POVIDONE**

**Synonyms:** Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; 1-vinyl-2-pyrrolidinone polymer.

**Chemical name:** 1-Ethenyl-2-pyrrolidinone homopolymer

**Empherical formula:** (C6H9NO)n

**Functional category:** Disintegrant; dissolution aid; suspending agent; tablet binder.

**Applications in pharmaceutical formulations:** Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated insitu by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid dosage forms. Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

**Description:** Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are

manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

**Solubility:** Soluble in cold water, butanol, acetone, ethyl alcohol, poly ethylene glycol, and hydroxylethyl pyrrolidine.

**Stability and storage conditions:** Povidone darkens to some extent on heating at $150^0$C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–$130^0$C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

**7. SODIUM STARCH GLYCOLATE**

**Synonym:** Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

**Chemical name:** Sodium carboxymethyl starch

**Functional category:** Tablet and capsule disintegrant.

**Applications in pharmaceutical formulations:** Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet granulation processes.

**Description:** Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 mm in diameter, with some less-spherical granules ranging from 10–35 mm in diameter.

**Solubilty:** Practically insoluble in water, insoluble in most organic solvents.

**Stability and storage conditions:** Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3–5 years if it is stored at moderate temperatures and humidity.

## 8.COLLOIDAL SILICON DIOXIDE

**Synonyms:** Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed; Wacker HDK.

**Chemical name:** Silica

**Empherical formula:** SiO2

**Functional category:** Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

**Applications in pharmaceutical formulations:** Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products; Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tabletting. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity; In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders. Colloidal silicon dioxide is frequently added to suppository formulations

containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. Colloidal silicone dioxide is also used as an adsorbent during the preparation of wax microspheres; as a thickening agent for topical preparations; and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

**Description:** Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-whitecolored, odorless, tasteless, nongritty amorphous powder.

**Solubility:** Practically insoluble in water and in acids, soluble in hot solutions of alkali hydroxides.

**Stability and storage conditions:** Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0-7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates.Colloidal silicon dioxide powder should be stored in a well-closed container. Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopicity.

**9. STEARIC ACID**

**Synonyms:** Cetylacetic acid; Crodacid; E570; Edenor; Emersol; Hystrene; Industrene; Kortacid ; Pearl Steric; Pristerene; stereophonic acid; Tegostearic.

**Chemical name:** Octadecanoic acid

**Empherical formula:** C18H36O2

**Functional category:** Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

**Applications in pharmaceutical formulations:** Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant; although it may also be used as a binder or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used as a sustained-release drug carrier. In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams. The partially neutralized stearic acid forms a creamy base when mixed with 5–15 times its own weight of aqueous liquid; the appearance and plasticity of the cream being determined by the proportion of alkali used. Stearic acid is used as the hardening agent in glycerin suppositories. Stearic acid is also widely used in cosmetics and food products.

**Description:** Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor and taste suggesting tallow.

**Solubility:** Soluble in water, diethyl ether, acetone, ethanol, dimethyl formamide.

**Stability and storage conditions:** Stearic acid is a stable material; an antioxidant may also be added to it; The bulk material should be stored in a well-closed container in a cool, dry place.

# METERIALS & METHODS

**Table.2: MATERIALS USED:**

| S.No. | Ingredients | Category | Source |
|---|---|---|---|
| 1 | Olmesartan medoxomil | Drug | Celon labs pvt ltd. (Hyderabad) |
| 2 | Micro crystalline cellulose | Diluent | Niebrim chemicals ltd. (Banglore) |
| 3 | Lactose monohydrate | Diluent | Vijilakpharma (Mumbai) |
| 4 | Povidone | Binding agent | ISP technologies (Banglore) |
| 5 | Crospovidone | Disintegrant | Vijilakpharma (Mumbai) |
| 6 | Croscaramellose sodium | Disintegrant | Niebrim chemicals (Banglore) |
| 7 | Sodium starch glycolate | Disintegrant | SD fine chemicals (Hyderabad) |
| 8 | Magnesium stearate | Lubricant | Niebrim chemicals (Banglore) |
| 9 | Colloidal silicon dioxide | Glidant | Venkar labs pvt limited (Hyderabad) |
| 10 | Stearic acid | Lubricant | Signet chemicals (Mumbai) |

**Table.3: EQUIPMENTS USED:**

| NAME OF INSTRUMENT | VENDOR |
|---|---|
| Digital balance | Wiggenhauser (Japan) |
| Electronic balance | Essae (Germany) |
| Vibratory sifter | SSPM (Mumbai) |
| Rapid mixer granulator(RMG) | SSPM (Mumbai) |
| Hot air oven | Heat control instruments & Co. (Switzerland) |
| Friabilator USP | Electrolab (Japan) |
| UV-visible spectrophotometer | Perkin Elmer (Germany) |
| JR moisture balance | Servell instruments (Banglore) |
| Multi mill | SSPM (Mumbai) |
| Octagonal blender | SSPM (Mumbai) |
| 8 and 16 station tablet compression machine | Rimek (Japan) |
| Disintegration Tester (USP) | Tab Machines (Banglore) |
| Mechanical Stirrer | Remi Motors (Mumbai) |
| VernierCalliperse | Mitutoyo Corporation |
| FT-IR spectrophotometer | Jasco (Japan) |
| Dissolution Apparatus (USP) Type-II | Electrolab (Mumbai) |
| Hardness Tester | Tab Machines (Kolkata) |
| Tap density tester | Campbell electronics (Mumbai) |

**PREFORMULATION STUDIES:**

**DRUG-EXCIPIENTS COMPABILITY STUDIES:**

Drug was mixed with excipients in different ratios. About 5gm of blend was prepared, which were kept in 10ml white colored glass vials and packed properly. These vials are exposed to room temperature and 25±2$^{o}$c/60±5% RH. Observations for physical appearance were made at zero weeks to 1 month, then the samples were withdrawn for analysis of appearance. The drug-excipient interaction was investigated by FT-IR.

**FT-IR SPECTROSCOPY:**

Drug and excipients compatibility study is done by fourier transform infrared (FT-IR) spectroscopy. FT-IR spectra were obtained by using an FT-IR spectroscopy-410 (jasco-japan). The samples (pure drug and final formulation in 1:1 ratio) were previously ground and mixed thoroughly with KBr, an infrared transparent matrix at 1:5 (sample /KBr) ratio respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 mins in a hydraulic press (40 scans were obtained at a resolution 4cm$^{-1}$ from 4600-300 cm$^{-1}$).

The compatibility studies provide the frame work for the drugs combination with the excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets.

**SOLUBILITY:**

1part of drug was taken and dissolved in 50ml of water, and found that the drug was insoluble in water, then 1 part of drug was taken and dissolved in 10ml of chloroform, the drug was soluble in chloroform and 1part of drug was taken and dissolved in 10ml of glacial acetic acid, the drug was found to be soluble then 1part of drug was taken and dissolved in 10ml of acidic buffer (pH 1.2), the drug was freely soluble in acidic buffer.

**BULK DENSITY DETERMINATION:**

Exactly 50 gm of drug was weighed on digital balance and transferred into a 100 ml measuring cylinder. The volume occupied by the drug was recorded as the bulk volume. This is the bulk

volume and the bulk density was calculated. It is expressed in gm/cc and is given by, Db (gm/cc) $= \frac{M}{Vb}$, Where, M is the mass of drug in gm and Vb is the bulk volume of the drug**.**

Bulk density was calculated using the formula.

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

**TAPPED DENSITY DETERMINATION:**

An accurately weighed quantity of the Olmesartan medoxomil blend (W), was carefully poured into the graduated cylinder and the volume ($V_o$) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume ($V_f$) was measured and continued operation till the two consecutive readings were equal. The volume of blend was used to calculate the tapped density, Hausner's ratio and Carr's Index.

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Tapped volume of granules}}$$

**ANGLE OF REPOSE:**

A cylinder was taken, one end it is open and other end closed. The granules then poured in to the cylinder nearly (10-20gms) and the tube was gradually withdrawn without any shaking to form heaping on the horizontal surface, once the heap is formed the height of the heap was measured the circumference of the circle was measured. From these the Θ was determined.

The angle of repose was calculated by using the formula given below.

Angle of Repose ($\theta$) = $\tan^{-1}$ (h/r)

Where, h = height of pile

r = radius of the base of the pile

θ = angle of repose

**CARR'S INDEX:**

Carr's index is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics.

Carr's index was calculated by using the formula:

$$\text{Carr's Index} = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} \text{ X } 100$$

**HAUSNER'S RATIO:**

Hausner's Ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. Hausner's ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density.

Hauser's ratio was calculated by using the formula.

Hauser's Ratio: Tapped density / Bulk density

Hauser's Ratio: $V_F/V_O$

Where, $V_0$ = Initial volume

$V_f$ = Final volume

**MOISTURE CONTENT (OR) WATER BY KF:**

Around 50ml of methanol was taken in titration vessel and titrated with Karl Fischer reagent to end point. In a dry mortar, the pellets were ground to fine powder. Weighed accurately about 0.5g of the sample, transferred quickly to the titration vessel, stiff to dissolve and titrated with Karl Fischer reagent to end point, pale yellow color was observed.

**Calculation:**

$$\text{Moisture content} = \frac{V \times F \times 100}{\text{Weight of sample in mg}}$$

Where, F = factor of Karl Fischer reagent.

V = volume in ml of Karl Fischer reagent consumed for sample titration.

**FORMULATION OF IMMEDIATE RELEASE OLMESARTAN MEDOXOMIL TABLETS:**

**Wet granulation method:**

**Step I Sifting of Raw Materials:**

Olmesartan medoxomil, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, crospovidine, sodium starch glycolate were sifted through #40 mesh and mixed in poly bag for 15 mins.

**Step II Preparation of Binder solution:**

18gms of povidone was dissolved in sufficient quantity of water and mixed well by using mechanical stirrer for the preparation of binder solution.

**Step III Wet Granulation:**

Transferred the sifted olmesartan, microcrystalline cellulose, croscarmellose sodium, crospovidone, sodium starch glycolate, lactose monohydrate into Rapid mixer granulator. Dry mixed the powders present in Rapid Mixer Granulator for 5 minutes without chopper on. Added the binder solution to dry mixed powder under beater mixing. After 5 minutes of mixing switch on the chopper at high speed which will enable to break the lumps into granules. If required add additional quantity of Purified water.

**Step IV Drying:**

The granules were dried at 65°C inlet temperature in fluid bed drier. After 20 minutes of drying, removed the bowel from Fluid bed drier and mixed with SS 316 rod. Started drying again till the exhaust temperature was 38°C then stoped the drying process. Sample was taken from the fluid bed drier bowl and checked the Loss on Drying by using LOD apparatus at 105°C till constant weight. It should be between 1.5-3.5%.

**Sifting of extra granular material:**

lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, crospovidine, sodium starch glycolate, were sifted through #40 mesh and mixed in poly bag for 15 mins.

**Step V Pre Blending and Final Blending:**

Dried, sized granules were loaded into the Octagonal blender then loaded the sifted extra granular raw materials into the blender and blended for 15-20 minutes and then Magnesium Stearate, colloidal silica, stearic acid were loaded into Octagonal blender, Blended for 5 minutes.

**Step VI Compression:**

The tablet machine was fixed with D type, 1.5×8mm round flat bevel edged tooling to the 16 station rotary tablet machine as per the SOP. Finally the lubricated granules were then compressed in to tablets on a 16 station rotary machine to get a 400mg weight.

**Table.4: Formula for immediate release formulation**

| Ingredients | Batch No: (mg/tab) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** | **F10** |
| **INTRA-GRANULATION** | | | | | | | | | | |
| Olmesartan medoxomil | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Micro crystalline cellulose | 188 | - | 94 | - | 94 | 92 | 92 | 92 | 92 | 92 |
| Lactose monohydrate | - | 140 | - | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| Povidone | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| Crospovidone | - | - | - | - | - | - | - | 7 | - | - |
| Croscaramellose sodium | - | - | - | - | - | - | - | - | 7 | 7 |
| Sodium starch glycolate | - | - | - | - | - | - | 7 | - | - | - |
| Purified Water | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| **EXTRA-GRANULATION** | | | | | | | | | | |
| Micro crystalline cellulose | - | 188 | 94 | 188 | 94 | 92 | 92 | 92 | 92 | 92 |
| Lactose monohydrate | 140 | - | 140 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| Crospovidone | - | - | - | - | - | - | - | 7 | - | - |
| Croscaramellose sodium | - | - | - | - | - | - | - | - | 7 | 7 |
| Sodium starch glycolate | 10 | 10 | 10 | 10 | 10 | 14 | 7 | - | - | - |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | - |
| Colloidal silicon dioxide | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Stearic acid | - | - | - | - | - | - | - | - | - | 2.5 |
| TOTAL | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

# EVALUATION OF COMPRESSED TABLETS

The evaluation of tablets includes, the nature of the active ingredient (identification), expected amount (assay), purity (related compounds), and uniformity of the amount of drug from tablet to tablet (uniformity of dosage units).
In addition to these tests, some other tests such as friability, hardness, disintegration, etc. are also conducted.

## PHYSICAL APPEARANCE:

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color, presence or absence of odor, taste, surface texture and consistency of any identification marks.

## HARDNESS TESTING:

Hardness of the tablet was determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture. When a tablet is placed in a barrel it breaks at a force of compression on a tablet by guaze in the barrel fracture. The tablet hardness of 5 kg is considered as suitable for handling the tablet.

## THICKNESS:

10 tablets were measured for their thickness and diameter with a Caliper, Thickness Gauge. Average thickness and diameter were calculated.

## FRIABILITY:

The friability of tablets was determined by Roche Friabillator. 20 tablets were taken and weighed. After weighing, the tablets were placed in the Roche Friabillator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for minutes dropping the from a distance of six inches with each revolution. After operation the tablets were de-dusted and reweighed.

Friability was determined by

$F = 100 (1-W_o/ W_t)$

Where,

$W_o$ = weight of tablets before friability test.

$W_t$ = weight of tablets after friability test.

**DISINTEGRATION TIME:**

6 tablets were taken and placed each tablet in each tube of 6 tubes with a base of metal sieve of a basket assembly of USP disintegration apparatus and operated. The apparatus temperature was maintained at $37^0 \pm 0.5^0$c. The medium used is 0.1N Hcl (pH 1.2) buffer medium. The tablets are intended to disintegrate into coarse particles in the medium in specific time were noted and comparision to I.P standard.

**UNIFORMITY OF DOSAGE FORMS:**

This test was conducted to establish consistency in the content of active ingredient from tablet to tablet. There are generally two approaches for establishing this:

- Weight variation
- Content uniformity

**Weight Variation:**

20 tablets were individually weighed, calculated the average weight, and compared the individual tablet weights to the average. The tablets met the USP tests that were not more than 2 tablets were outside the percentage limit and no tablets differed by more than 2 times the percentage limit. The maximum percentage difference allowed is 5% for average weight of tablets more than 324mg.

**Content Uniformity:**

In this test, 20 tablets were randomly selected contained for drug, and 10 the tablets olmesartan medoxomil should contain not less than 85.0 % and not more than 115.0 % of the label claim. If one unit outside the range of 85 to 115% of the label claim and no units is outside 75 to 125% or if RSD> 6% or if both conditions prevail, test 20 additional units.

**ASSAY:**

**Standard preparation:**

40mg of accurately weighed olmesartan medoxomil powder was taken and transferred in to 100ml volumetric flask. Initially 10ml of 0.1N Hcl (pH 1.2) solution was added and shaken for 10min. Then, volume was made up to 100ml with 0.1N Hcl (pH 1.2) solution. This solution was filtered, and 1ml of filtrate was suitably diluted to 10ml with same diluent to obtain concentration of 40 μg $mL^{-1}$ respectively and analysed by using UV-visible spectrophotometer, measured at 265 nm.

**Sample preparation:**

Twenty tablets were powdered and weight equivalent to 40mg of olmesartan medoxomil. Powder was transferred in to 100ml volumetric flask. Initially 10ml of 0.1N Hcl (pH 1.2) solution was added and shaken for 10min. Then, volume was made up to 100ml with 0.1N Hcl (pH 1.2) solution. This solution was filtered, and 1ml of filtrate was suitably diluted to 10ml with same diluent to obtain concentration of 40 μg $mL^{-1}$ respectively and analysed. Absorbance of each sample was measured at 265 nm using UV-visible spectrophotometer. The drug content of the sample was estimated from their standard curve.

**STANDARD CALIBRATION CURVE:**

**Stock solution:**

Standard stock solution was prepared by weighing out 100mg of olmesartan and transferred to 100ml volumetric flask. It was dissolved in 0.1N Hcl (pH 1.2) solution and made up to volume to get a concentration of 1mg/ml. spectral characteristics of olmesartan were studied by taking concentrations of 10, 20, 30, 40, 50 mcg/ml, final concentrations of 5, 10, 15, 20, 25, 30, 35, 40,

45 µg $ml^{-1}$ obtained scanned by UV-visible spectrophotometer at λmax of 265nm. Calibration curve of absorbance versus concentration were studied by taking concentration ranging from 1-40mcg/ml and data revealed that Beer's law was obeyed between concentration range of 5-45mcg/ml.

***In-vitro* DISSOLUTION TEST:**

In-vitro drug release studies for the prepared tablets were performed by USP dissolution apparatus, type-2 (paddle) and volume was made up to 900ml using 0.1N Hcl (pH 1.2) buffer. The apparatus is maintained at temperature $37^0 \pm 0.5^0$c. The rotation speed of paddle was adjusted to 50 rpm and the sample dilution was made 1ml to 10ml, replacing the volume by buffer medium with sampling time intervals of 15, 30, 45 and 60 min. The withdrawn samples were analysed by UV-visible spectrophotometer at 265nm.

**Preparation of 0.1N Hcl (pH 1.2) Buffer medium:**

8.5ml of concentrated Hcl was dissolved in 1000ml of distilled water, for the preparation of 0.1N Hcl (pH 1.2) Buffer medium.

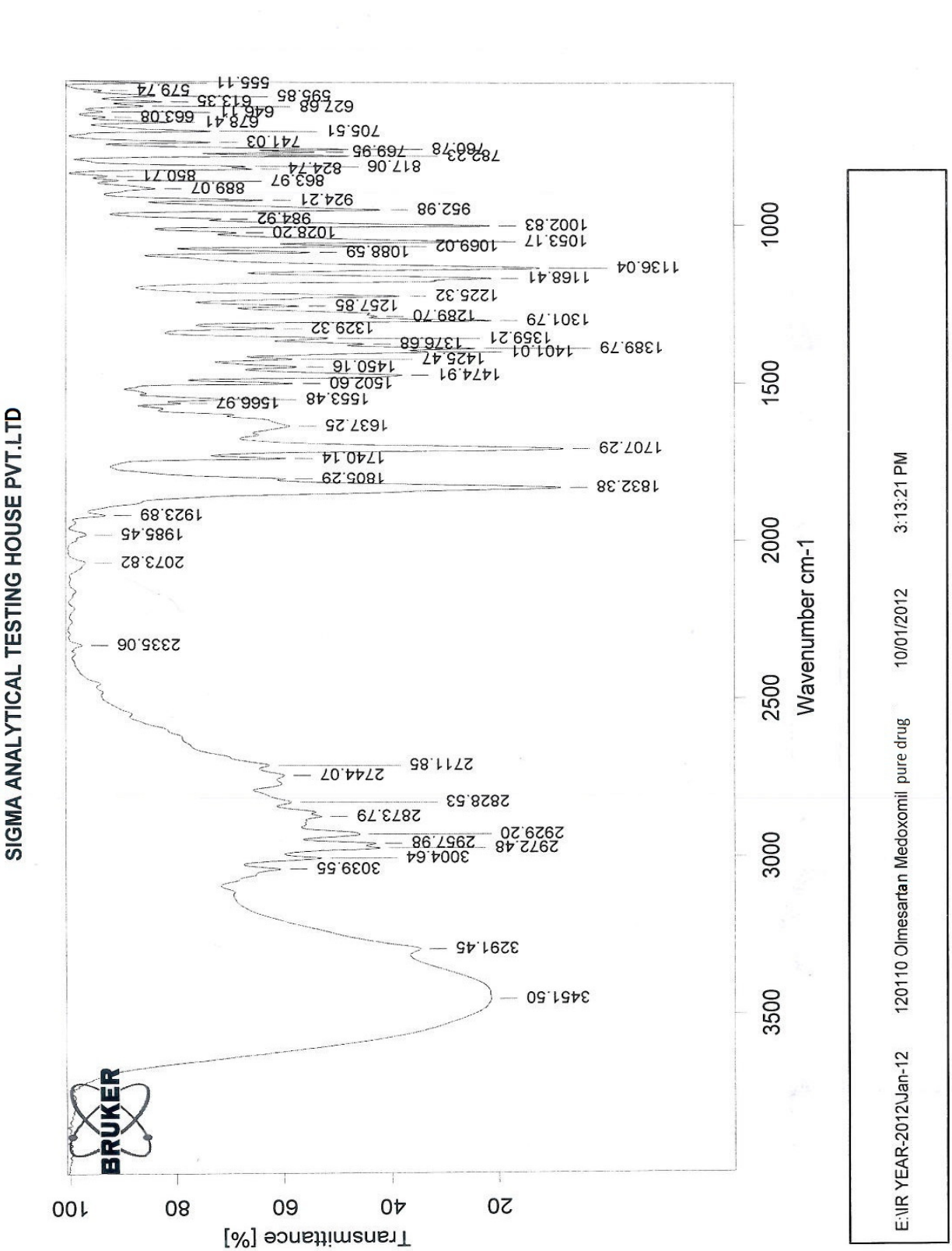
**STABILITY STUDIES:**

The final formulation, F8 tablets were placed in HDPE container and kept in stability chamber. These studies were carried out for 3 months at storage conditions of $25 \pm 2^0$c / 60 ± 5% RH. After completion of 3 months time, the samples were withdrawn and checked out for stability of the product.

# RESULTS

**Table.5: DRUG–EXCIPIENTS COMPATIBILITY STUDIES**

| S.NO | INGREDIENTS | RATIO | DESCRIPTION | |
|---|---|---|---|---|
| | | | Initial | After 1month at (25±2°c/60±5%RH) |
| 1 | Olmesartan medoxomil – API | 1 | White to off white powder | NCC |
| 2 | API + Micro crystalline cellulose | 1:5 | Off white coloured powder | NCC |
| 3 | API + Lactose monohydrate | 1:5 | White to off white powder | NCC |
| 4 | API + Povidone | 2:1 | White to creamy white powder | NCC |
| 5 | API + Crospovidone | 2:1 | White to creamy white powder | NCC |
| 6 | API + Croscaramellose sodium | 2:1 | Off white coloured powder | NCC |
| 7 | API + Sodium starch glycolate | 2:1 | White to off white powder | NCC |
| 8 | API + Magnesium stearate | 10:1 | Off white coloured powder | NCC |
| 9 | API + Colloidal silica | 10:1 | Off white coloured powder | NCC |
| 10 | API + Stearic acid | 10:1 | White to off white powder | NCC |


SIGMA ANALYTICAL TESTING HOUSE PVT.LTD
BRUKER
Transmittance [%]
100
80
60
40
20
Wavenumber cm-1
3500
3000
2500
2000
1500
1000
3451.50
3291.45
3039.55
3004.64
2972.48
2957.98
2929.20
2873.79
2828.53
2744.07
2711.85
2335.06
2073.82
1985.45
1923.89
1832.38
1805.29
1740.14
1707.29
1637.25
1566.97
1553.48
1502.60
1474.91
1450.16
1425.47
1401.01
1389.79
1376.58
1359.21
1329.32
1301.79
1289.70
1257.85
1225.32
1168.41
1136.04
1088.59
1069.02
1053.17
1028.20
1002.83
984.92
952.98
924.21
889.07
863.97
850.71
824.74
817.06
782.23
769.95
760.78
741.03
705.51
678.41
663.08
646.11
627.68
613.35
595.85
579.74
555.11
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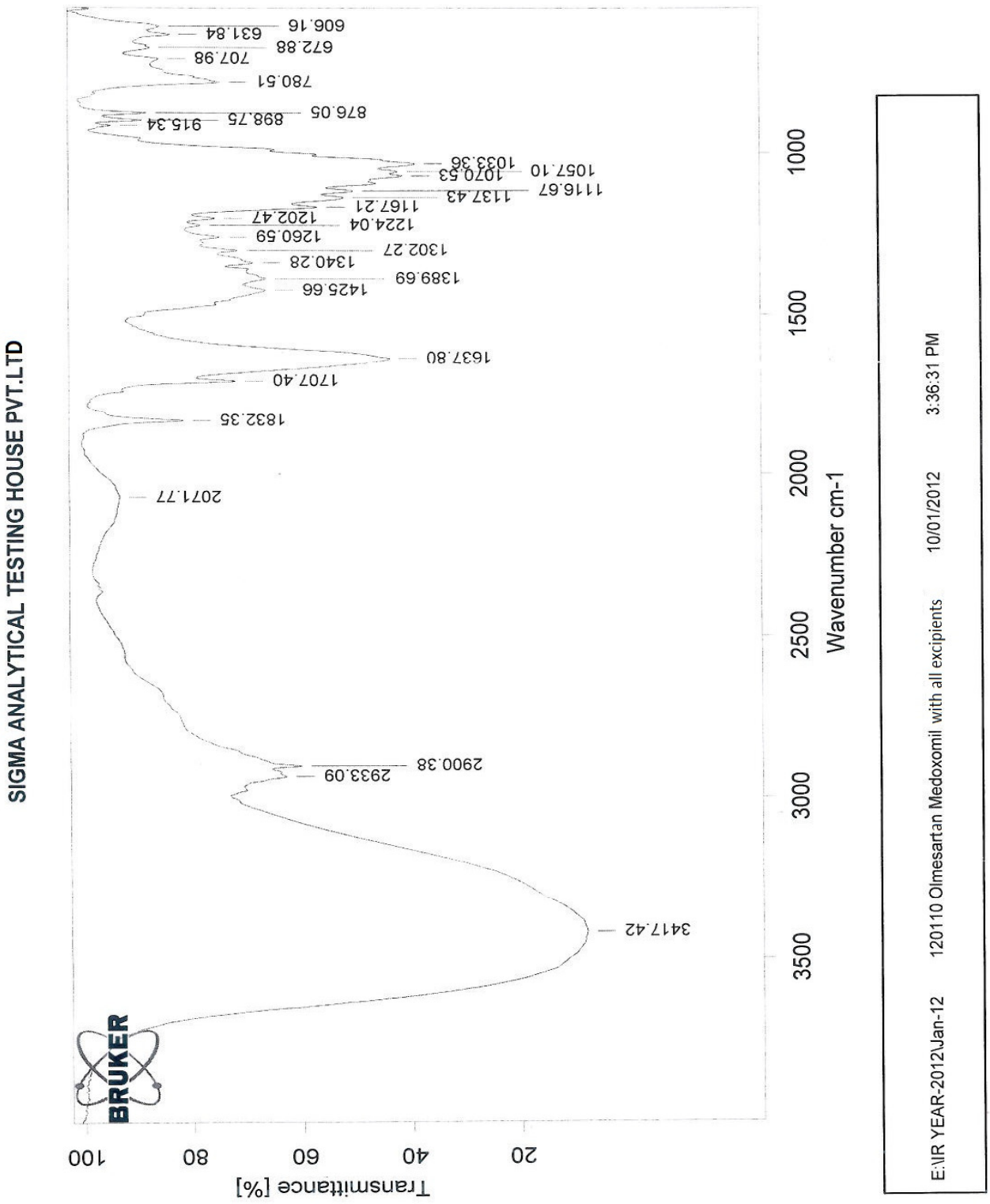
SIGMA ANALYTICAL TESTING HOUSE PVT.LTD
BRUKER
Transmittance [%]
100
80
60
40
20
Wavenumber cm-1
3500
3000
2500
2000
1500
1000
3417.42
2933.09
2900.38
2071.77
1832.35
1707.40
1637.80
1425.66
1389.69
1340.28
1302.27
1260.59
1224.04
1202.47
1167.21
1137.43
1116.67
1070.53
1057.10
1033.36
915.34
898.75
876.05
780.51
707.98
672.88
631.84
606.16
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**Preformulation studies for API:**

**Table.6: API RESULTS**

| | |
|---|---|
| **BULK DENSITY (gm/ml)** | **0.447** |
| **TAPPED DENSITY (gm/ml)** | **0.563** |
| **CARR'S INDEX (%)** | **20.60** |
| **HAUSNER'S RATIO** | **1.259** |
| **WATER CONTENT BY KF (%)** | **0.68** |
| **MOISTURE CONTENT (%)** | **0.71** |
| **ANGLE OF REPOSE (Ɵ)** | **31.2** |

**Table.7: BULK DENSITY, COMPRESSIBILITY INDEX, HAUSNER'S RATIO, ANGLE OF REPOSE OF OLMESARTAN MEDOXOMIL BLEND**

| FORMULATION CODE | BULK DENSITY (gm/ml) | TAP DENSITY (gm/ml) | COMPRESSIBILITY INDEX (%) | HAUSNER'S RATIO | MOISTURE CONTENT (%) | ANGLE OF REPOSE (degrees) |
|---|---|---|---|---|---|---|
| $F_1$ | 0.443±0.03 | 0.568±0.03 | 22.11±1.28 | 1.282±0.05 | 0.82 | 31.4±0.05 |
| $F_2$ | 0.449±0.04 | 0.558±0.04 | 20.53±1.33 | 1.242±0.09 | 0.96 | 32.3±0.06 |
| $F_3$ | 0.432±0.03 | 0.558±0.02 | 23.42±1.25 | 1.292±0.08 | 0.71 | 31.2±0.09 |
| $F_4$ | 0.488±0.05 | 0.643±0.03 | 24.10±1.37 | 1.317±0.04 | 0.94 | 27.2±0.08 |
| $F_5$ | 0.473±0.03 | 0.579±0.04 | 18.30±1.39 | 1.224±0.05 | 0.88 | 28.9±0.07 |
| $F_6$ | 0.463±0.04 | 0.583±0.05 | 20.58±1.36 | 1.259±0.06 | 0.63 | 29.3±0.04 |
| $F_7$ | 0.467±0.06 | 0.560±0.03 | 16.60±1.28 | 1.199±0.04 | 0.72 | 24.6±0.09 |
| $F_8$ | 0.461±0.02 | 0.532±0.02 | 13.34±0.98 | 1.154±0.02 | 0.62 | 24.8±0.03 |
| $F_9$ | 0.484±0.04 | 0.571±0.04 | 15.23±1.17 | 1.118±0.04 | 0.68 | 26.3±0.04 |
| $F_{10}$ | 0.469±0.03 | 0.559±0.02 | 16.10±1.26 | 1.192±0.03 | 0.79 | 27.3±0.08 |

**Table.8: HARDNESS OF OLMESARTAN MEDOXOMIL TABLETS FOR DIFFERENT FORMULATIONS**

| S.NO | FORMULATION CODE | HARDNESS OF TABLETS ($Kg/cm^2$) |
|---|---|---|
| 1 | F1 | 3.13±0.13 |
| 2 | F2 | 3.28±0.15 |
| 3 | F3 | 3.34±0.20 |
| 4 | F4 | 3.19±0.16 |
| 5 | F5 | 4.64±0.15 |
| 6 | F6 | 4.98±0.17 |
| 7 | F7 | 5.17±0.14 |
| 8 | F8 | 5.09±0.06 |
| 9 | F9 | 5.32±0.10 |
| 10 | F10 | 5.29±0.15 |

**Table.9: THICKNESS OF OLMESARTAN MEDOXOMIL TABLETS FOR DIFFERENT FORMULATION**

| S.NO | FORMULATION CODE | THICKNESS OF TABLETS(mm) |
|---|---|---|
| 1 | F1 | 4.12±0.014 |
| 2 | F2 | 4.18±0.018 |
| 3 | F3 | 4.21±0.017 |
| 4 | F4 | 4.34±0.014 |
| 5 | F5 | 4.27±0.016 |
| 6 | F6 | 3.99±0.015 |
| 7 | F7 | 4.08±0.013 |
| 8 | F8 | 4.11±0.006 |
| 9 | F9 | 4.17±0.008 |
| 10 | F10 | 4.28±0.007 |

**Table.10: FRIABILITY OF OLMESARTAN MEDOXOMIL TABLETS FOR DIFFERENT FORMULATIONS**

| S.NO | FORMULATION CODE | FRIABILITY OF TABLETS (%) |
|---|---|---|
| 1 | F1 | 0.812±0.023 |
| 2 | F2 | 0.998±0.054 |
| 3 | F3 | 1.016±0.041 |
| 4 | F4 | 0.967±0.033 |
| 5 | F5 | 0.513±0.053 |
| 6 | F6 | 0.597±0.031 |
| 7 | F7 | 0.432±0.026 |
| 8 | F8 | 0.397±0.017 |
| 9 | F9 | 0.416±0.021 |
| 10 | F10 | 0.579±0.028 |

**Table.11: AVERAGE WEIGHT OF OLMESARTAN MEDOXOMIL TABLETS FOR DIFFERENT FORMULATIONS**

| S.NO | FORMULATION CODE | AVERAGE WEIGHT OF TABLETS (mg) |
|---|---|---|
| 1 | F1 | 401.2±0.13 |
| 2 | F2 | 400.4±0.17 |
| 3 | F3 | 402.5±0.13 |
| 4 | F4 | 403.7±0.18 |
| 5 | F5 | 405.2±0.17 |
| 6 | F6 | 402.7±0.19 |
| 7 | F7 | 401.9±0.16 |
| 8 | F8 | 400.3±0.12 |
| 9 | F9 | 399.7±0.17 |
| 10 | F10 | 406.2±0.16 |

**Table.12: DISINTEGRATION TIME OF OLMESARTAN MEDOXOMIL TABLETS FOR DIFFERENT FORMULATIONS**

| S.NO | FORMULATION CODE | DISINTEGRATION OF TABLETS (min) |
|---|---|---|
| 1 | F1 | 2.32±0.06 |
| 2 | F2 | 2.19±0.04 |
| 3 | F3 | 1.57±0.05 |
| 4 | F4 | 2.02±0.08 |
| 5 | F5 | 1.24±0.07 |
| 6 | F6 | 1.12±0.09 |
| 7 | F7 | 0.58±0.08 |
| 8 | F8 | 0.39±0.02 |
| 9 | F9 | 0.48±0.05 |
| 10 | F10 | 0.51±0.04 |

**Table.13: ASSAY**

| SNO | FORMULATION CODE | PERCENTAGE DRUG CONTENT |
|---|---|---|
| 1 | F1 | 98.6±0.20 |
| 2 | F2 | 97.9±0.18 |
| 3 | F3 | 98.4±0.19 |
| 4 | F4 | 97.8±0.17 |
| 5 | F5 | 98.1±0.25 |
| 6 | F6 | 98.9±0.23 |
| 7 | F7 | 99.2±0.22 |
| 8 | F8 | 99.8±0.16 |
| 9 | F9 | 99.5±0.19 |
| 10 | F10 | 98.7±0.18 |

**Table.14: STANDARD CURVE OF OLMESARTAN MEDOXOMIL IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | CONCENTRATION (µg/ml) | ABSORBANCE AT 265 nm |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 0.184 |
| 3 | 10 | 0.348 |
| 4 | 15 | 0.526 |
| 5 | 20 | 0.721 |
| 6 | 25 | 0.901 |
| 7 | 30 | 1.112 |
| 8 | 35 | 1.346 |
| 9 | 40 | 1.534 |
| 10 | 45 | 1.732 |

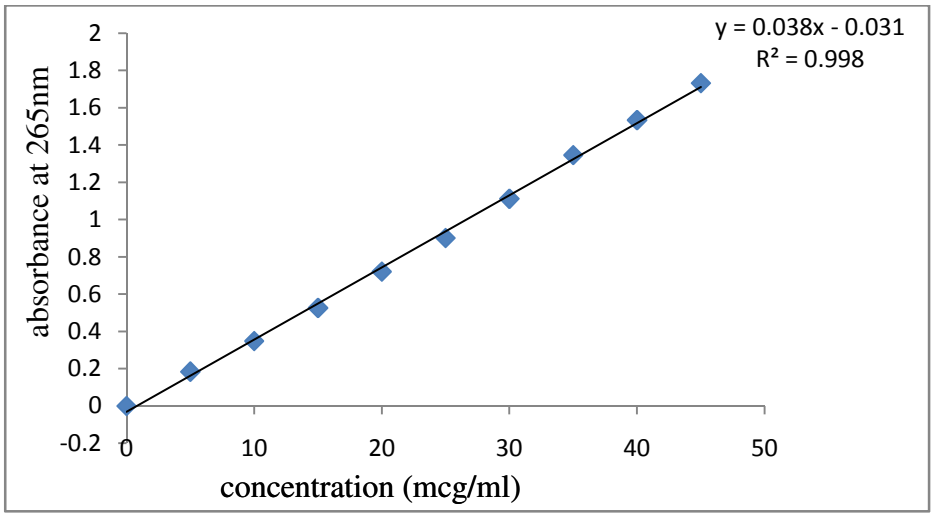


**Fig.3: STANDARD CALIBRATION CURVE OF OLMESARTAN MEDOXOMIL IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.15: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_1$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 34.6 ± 0.13 |
| 3 | 30 | 51.3 ± 0.20 |
| 4 | 45 | 71.2 ± 0.18 |
| 5 | 60 | 84.2 ± 0.14 |

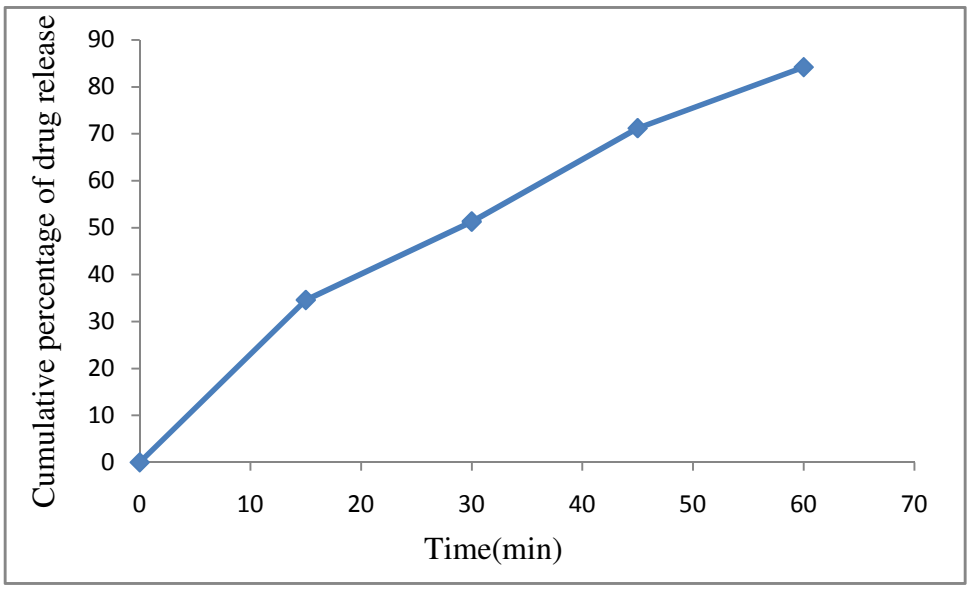


**Fig.4: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_1$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.16: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_2$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 32.4 ± 0.15 |
| 3 | 30 | 49.3 ± 0.11 |
| 4 | 45 | 70.8 ± 0.17 |
| 5 | 60 | 82.9 ± 0.13 |

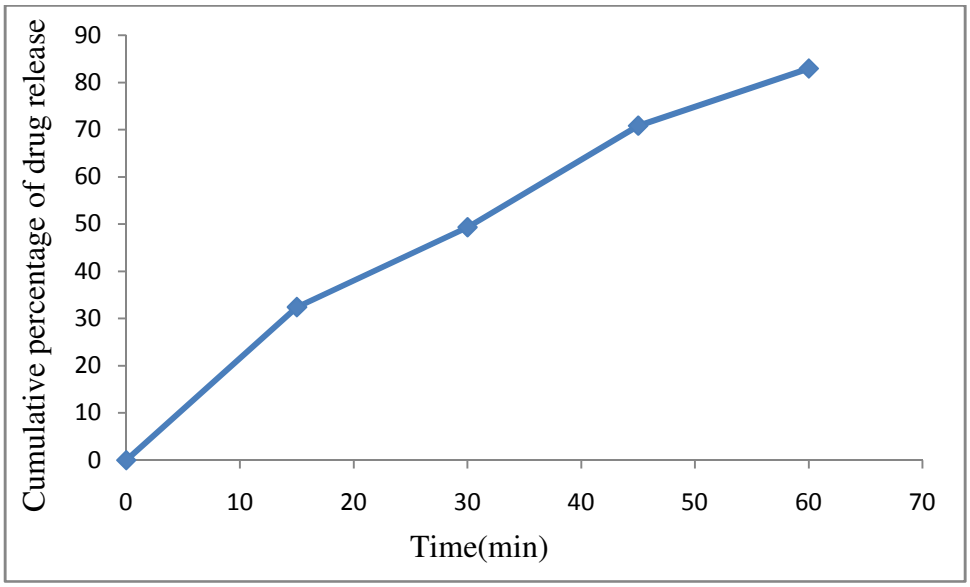


**Fig.5: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_2$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.17: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_3$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 35.2 $\pm$ 0.13 |
| 3 | 30 | 51.0 $\pm$ 0.19 |
| 4 | 45 | 69.8 $\pm$ 0.15 |
| 5 | 60 | 83.7 $\pm$ 0.17 |

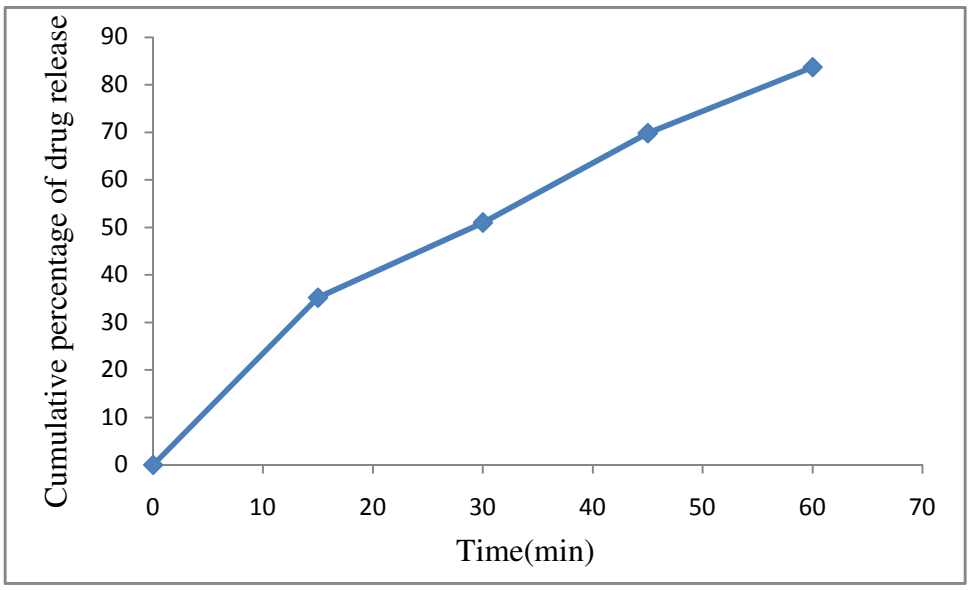


**Fig.6: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_3$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.18: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_4$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 32.9 ± 0.16 |
| 3 | 30 | 51.3 ± 0.14 |
| 4 | 45 | 73.8 ± 0.18 |
| 5 | 60 | 86.9 ± 0.17 |

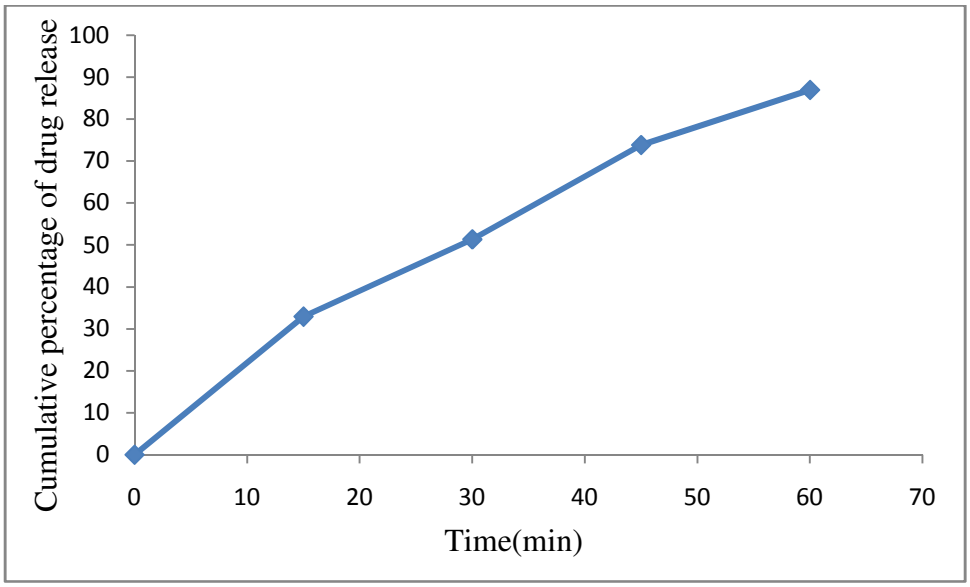


**Fig.7: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_4$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.19: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_5$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 40.7 ± 0.13 |
| 3 | 30 | 59.3 ± 0.15 |
| 4 | 45 | 80.1 ± 0.16 |
| 5 | 60 | 91.4 ± 0.12 |

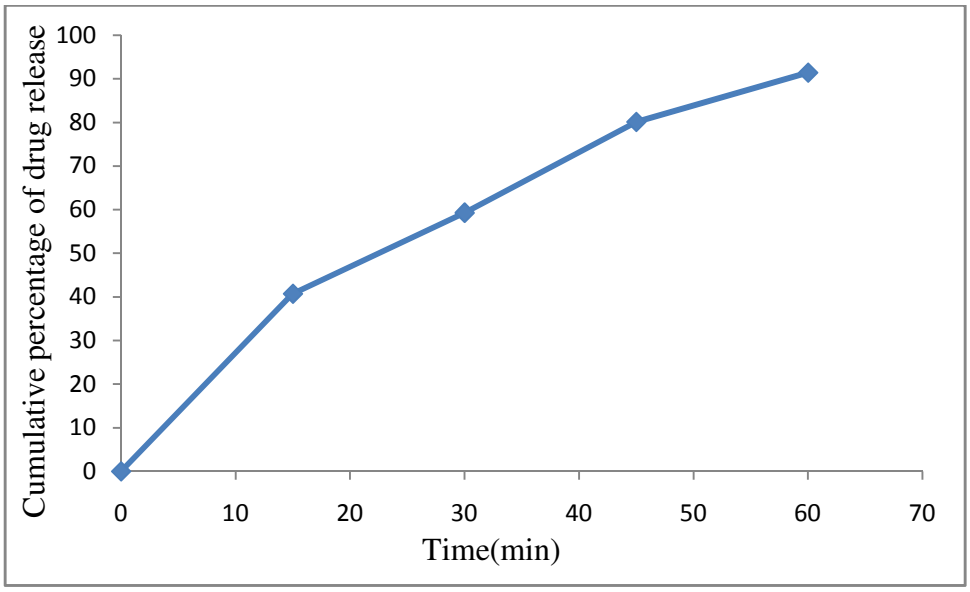


**Fig.8: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_5$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.20: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_6$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 41.8 ± 0.17 |
| 3 | 30 | 60.3 ± 0.14 |
| 4 | 45 | 84.6 ± 0.12 |
| 5 | 60 | 92.8 ± 0.11 |

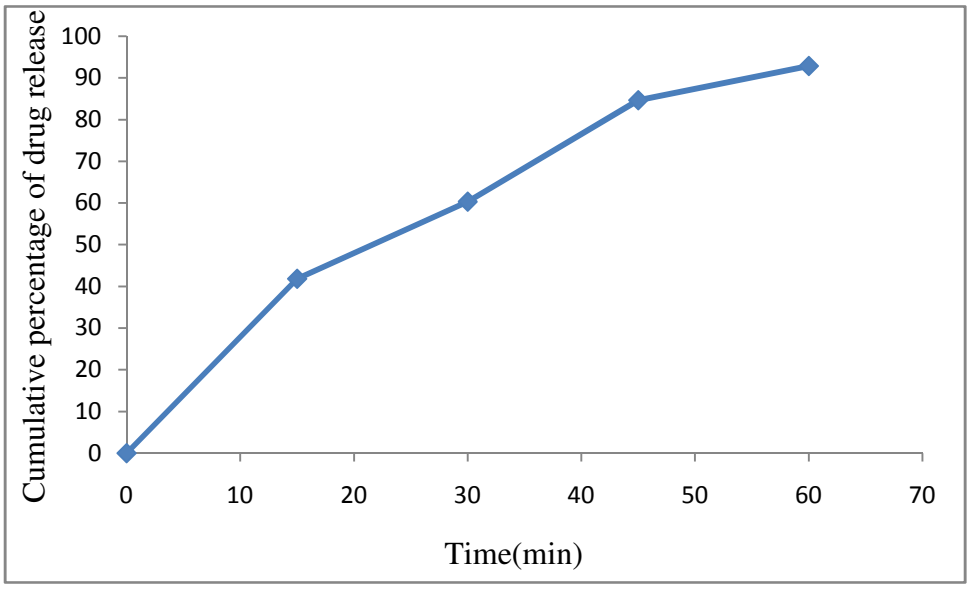


**Fig.9: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_6$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.21: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_7$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 40.9 ± 0.12 |
| 3 | 30 | 62.3 ± 0.19 |
| 4 | 45 | 86.9 ± 0.18 |
| 5 | 60 | 95.8 ± 0.17 |

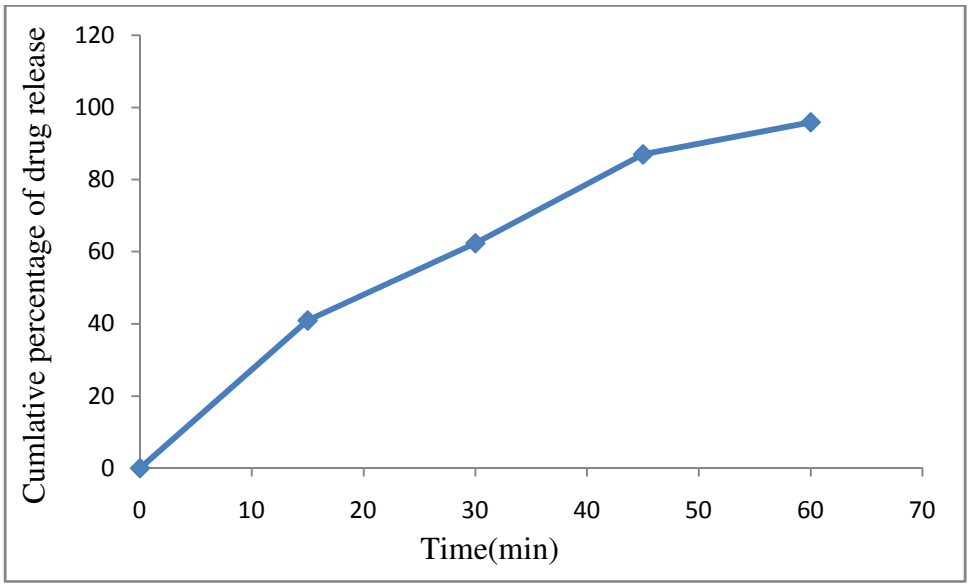


**Fig.10: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_7$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.22: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_8$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 55.6 ± 0.12 |
| 3 | 30 | 81.4 ± 0.14 |
| 4 | 45 | 93.6 ± 0.16 |
| 5 | 60 | 99.5 ± 0.15 |

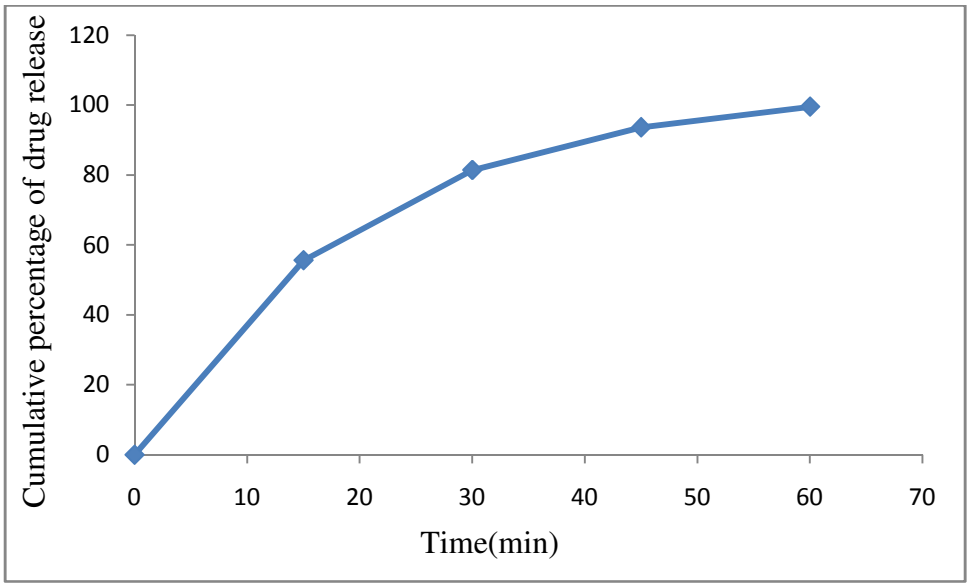


**Fig.11: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_8$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.23: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_9$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 50.4 ± 0.11 |
| 3 | 30 | 77.6 ± 0.18 |
| 4 | 45 | 86.3 ± 0.17 |
| 5 | 60 | 94.9 ± 0.15 |

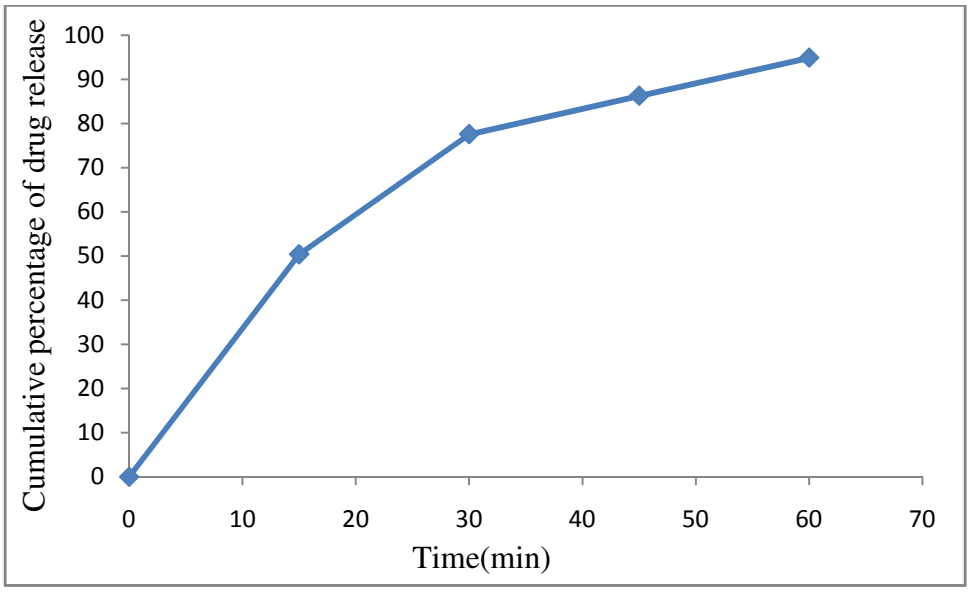


**Fig.12: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_9$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**Table.24: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_{10}$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

| S.NO | TIME IN MINUTES | CUMULATIVE PERCENTAGE OF DRUG RELEASED |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 15 | 50.9 ± 0.16 |
| 3 | 30 | 78.6 ± 0.11 |
| 4 | 45 | 88.3 ± 0.19 |
| 5 | 60 | 96.5 ± 0.15 |

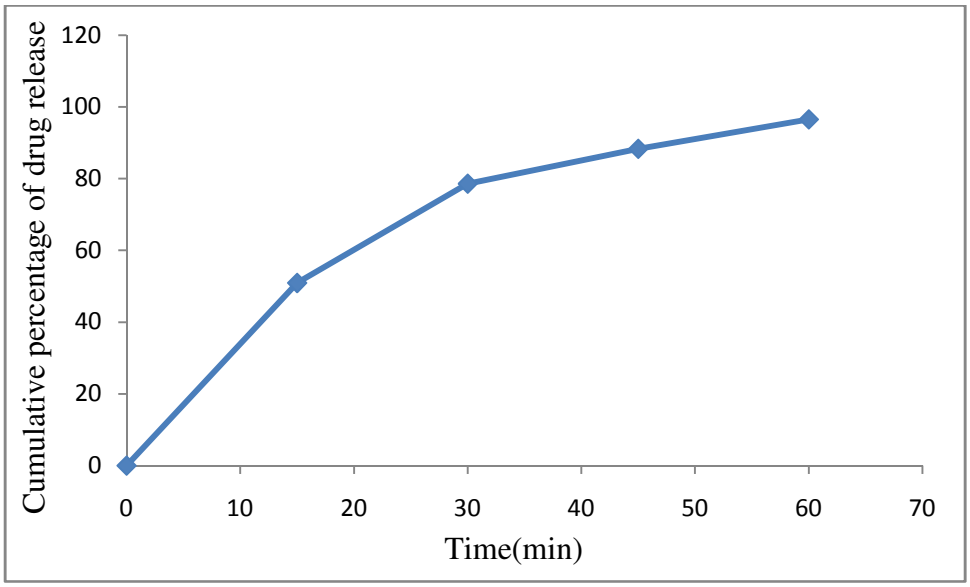


**Fig.13: INVITRO DISSOLUTION PROFILE OF FORMULATION $F_{10}$ IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

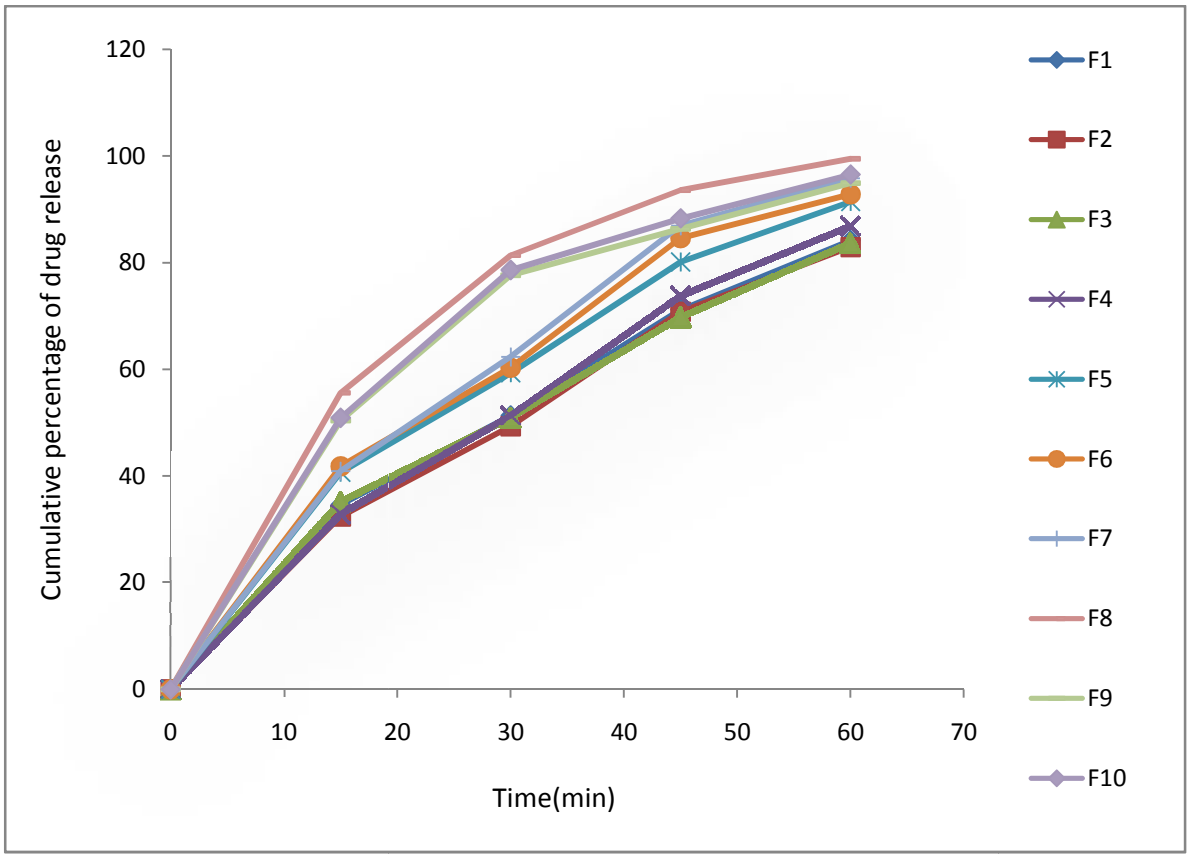


**Fig.14: COMPARISON OF INVITRO DISSOLUTION PROFILES OF ALL FORMULATIONS ($F_1$ TO $F_{10}$) TO THE INNOVATOR IN 0.1N HCL (PH 1.2) BUFFER MEDIUM**

**STABILITY STUDIES:**

**Table.25: Physical and chemical parameters of Olmesartan medoxomil tablets of formulation F8 after one month and 3 months at 25±2°C/60±5% RH**

| Parameter | Initial | After 1 month | After 3 months |
|---|---|---|---|
| Colour & Appearance | White to white off round shaped tablets | White to white off round shaped tablets | White to white off round shaped tablets |
| Assay (%) | 99.8±0.16 | 99.8±0.17 | 99.7±0.19 |
| Avg.weight (mg) | 400.3±0.12 | 400.1±0.14 | 399.8±0.16 |
| Hardness ($kg/cm^2$) | 5.09±0.06 | 5.06±0.08 | 5.02±0.09 |
| Thickness (mm) | 4.11±0.006 | 4.11±0.007 | 4.10±0.009 |
| Friability (%) | 0.397±0.017 | 0.422±0.021 | 0.435±0.027 |

**Table.26: Dissolution profiles of Olmesartan medoxomil tablets from formulation F8 after one month and 3 months at 25°C/60% RH**

| Time interval (min) | Cumulative Percentage drug release | | |
|---|---|---|---|
| | **Initial** | **After 1 month** | **After 3 months** |
| 0 | 0 | 0 | 0 |
| 15 | 55.6 ± 0.12 | 54.8 ± 0.18 | 53.6 ± 0.17 |
| 30 | 81.4 ± 0.14 | 79.6 ± 0.15 | 78.9 ± 0.19 |
| 45 | 93.6 ± 0.16 | 91.9 ± 0.11 | 90.1 ± 0.15 |
| 60 | 99.5 ± 0.15 | 98.3 ± 0.19 | 97.6 ± 0.13 |

# DISCUSSION

Immediate release tablet of Olmesartan medoxomil were successfully prepared by wet granulation using excipients microcrystalline cellulose, lactose monohydrate, povidone, crospovidone, croscaramellose sodium, sodium starch glycolate, magnesium stearate, colloidal silica, stearic acid. Formulations were evaluated for pre and post compression parameters.

The FT-IR spectral analysis showed that there was no change of any characteristic peaks of pure drug olmesartan and excipients, which confirmed that the absence of chemical interaction between drug and excipients.

The granules of the tablets were prepared by wet granulation method and evaluated for various physicochemical characteristics. The granules of different formulation were evaluated for angle of repose, bulk density and tapped density, compressibility index, hausner's ratio. It showed that the results of all formulations of the granules were within limits and thus it confirmed that the granules have good flow property except F1, F2, F3 & F4. In these first four formulations microcrystalline cellulose and lactose monohydrate were incorporated unequally in both intra and extra granulation, have poor compressibility index.

The post compression parameters such as thickness, disintegration time, hardness, friability, drug release, weight variation and drug content showed that the results of all formulations were in limits except F1, F2, F3 & F4.

Formulations F1, F2, F3 & F4 have poor flow property. So that the physico-chemical parameters such as hardness of the tablet was not found satisfactory. And the % friability of the tablet was out of the pharmacopoeial limit. Dissolution parameter for batches F1, F2, F3 & F4 was not satisfactory. In formulations from F5 microcrystalline cellulose and lactose monohydrate were incorporated equally of (1:1) ratio in both intra and extra granulation. So that the physico-chemical parameters such as hardness and % friability of the tablet were improved. The percentage drug release of formulation F5 was improved to be 91.4% at the end of 60min. Table no.19.

In F6 for the improvement of % drug release, we increased the concentration of sodium starch glycolate in extragranulation. The percentage drug release of formulation F6 was improved to be

92.8% at the end of 60min. Table no.20. For further improvement of drug release in F7 incorporated the superdisintegrant sodium starch glycolate equally in both intra and extra granulation. The percentage drug release of formulation F7 was to be 95.8% at the end of 60min. Table no.21.

In F8 used the super disintegrant crospovidone were incorporated equally between the intra and extragranulation. The percentage drug release of formulation F8 was to be 99.5% at the end of 60min. Table no.22.

In F9 & F10 the effect of other super disintegrant, croscaramellose sodium were studied respectively with other super disintegrants such as crospovidone and sodium starch glycolate. In this crospovidone showed better percentage drug release than croscaramellose sodium and sodium starch glycolate. In formulation F10 release rate at the end of 60min was slightly improved when compared to F9 and we incorporated stearic acid instead of magnesium stearate in extragranulation in order to improve flow property but there was not found any changes when compared to other formulations.

From the release profile result crospovidone can release drug faster compared to croscaramellose sodium and sodium starch glycolate. Crospovidone > Croscaramellose sodium > Sodium starch glycolate.

In the present work efforts have been made to develop Olmesartan medoxomil immediate release tablets as an approach to enhance the drug release profile using Superdisintegrants. The results showed that the release of the drug was depended on different superdisintegrants used, in that crospovidone can release drug faster compared to croscaramellose sodium and sodium starch glycolate. And the best formulation (F8) containing 3.5% crospovidone showed minimum disintegration time and better drug release profile as compared to other formulations.

# CONCLUSION

Olmesartan medoxomil tablets were formulated by wet granulation method using lactose monohydrate as diluent, MCC as diluent, povidone as binding agent, crospovidone, croscaramellose sodium & sodium starch glycolate as super disintegrating agents and colloidal silica as glidant, magnesium stearate & stearic acid as lubricant with good release profile for a specified period of time up to 1hr.

Compatibility studies were carried out for the physical mixture and the drug was found to be compatible with all excipients used in different formulations.

The granulation was compressed into tablets and were analysed for the parameters such as average weight, friability, thickness, hardness, disintegration and assay.

Formulation containing crospovidone (14mg) shows rapid rate of disintegration and dissolution when compared with other formulations.

The invitro dissolution profiles of F1 to F10 were found to have different percentage of drug release. The disintegration time for F8 tablets was relatively low (0.39min) and dissolution profile (99.5±0.15%) at the end of 60min. when compared to other formulations, F8 has better release profile and concluded that F8 was better formulation product.

The stability studies were conducted for F8 tablets for 3 months, which were found to be stable and concluded that formulation F8 was better stable product with good quality.

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